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PRINCIPLES  
OF  
INTERNAL MEDICINE

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# PRINCIPLES OF INTERNAL MEDICINE

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T. R. HARRISON

*Editor-in-Chief*

## EDITORS

PAUL B. BEESON

GEORGE W. THORN

WILLIAM H. RESNIK

M. M. WINTROBE



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To all those who have taught us, and  
especially to our younger colleagues who  
continue to teach and inspire us.



## Contributors

HARRY L. ALEXANDER, B.A., M.D.

Professor of Clinical Medicine, Washington University Medical School, St. Louis, Mo.

PAUL B. BEESON, M.D., C.M.

Professor and Chairman, Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

A. R. BEHNKE, B.A., M.D., M.S. (HON.)

Executive Officer, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.

PHILIP KRAMER BONDY, B.A., M.D.

Associate in Medicine, Emory University School of Medicine, Atlanta, Ga.

RICHARD B. CAPPS, B.S., M.D.

Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill.

JOHN S. CHAPMAN, B.A., M.A., M.D.

Clinical Assistant Professor of Medicine, Southwestern Medical School of the University of Texas, Dallas, Texas.

MARSHALL CLINTON, B.A., M.A., M.D.

Assistant Professor of Pharmacology, University of Buffalo School of Medicine, Buffalo, N. Y.

L. T. COGGESHALL, B.A., M.A., M.D., LL.D. (HON.)

Dean, Division of Biological Sciences, University of Chicago, Chicago, Ill.

LEWIS L. CORIELL, M.A., PH.D., M.D.

Assistant Professor of Immunology in Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pa.; Medical Director, Camden Municipal Hospital for Contagious Diseases, Camden, N. J.; Assistant Physician, The Children's Hospital of Philadelphia, Pa.

GUSTAVE J. DAMMIN, B.A., M.D.

Associate Professor of Pathology and Medicine, Washington University School of Medicine; Director of Laboratories, Barnes Hospital, St. Louis, Mo.

WILLIAM J. DARBY, M.D., PH.D.

Professor of Biochemistry, Assistant Professor of Medicine, Director of the Division of Nutrition, Vanderbilt University School of Medicine, Nashville, Tenn.

WILLIAM DOCK, B.S., M.D.

Professor of Medicine, Long Island College of Medicine; Director of Medicine, Kings County Hospital, Long Island College Division, Brooklyn, N. Y.

KENDALL EMERSON, JR., B.S., M.D.

Assistant Professor of Medicine, Harvard University Medical School; Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston, Mass.

GLADYS J. FASHENA, B.A., M.A., M.D.

Professor and Chairman, Department of Pediatrics, Southwestern Medical School of the University of Texas, Dallas, Texas.

A. E. FELLER, B.S., M.D.

Associate Professor of Preventive Medicine, Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

PETER H. FORSHAM, M.A., M.D.

Instructor of Medicine, Harvard University Medical School; Junior Associate in Medicine, Peter Bent Brigham Hospital, Boston, Mass.

HENRY M. FOX, B.S., M.D.

Assistant Professor of Psychiatry, Harvard University Medical School; Senior Associate in Psychiatry, Peter Bent Brigham Hospital, Boston, Mass.

WILLIAM F. FRIEDEWALD, B.S., M.D.

Professor of Bacteriology, Associate Professor of Medicine, Emory University School of Medicine; Physician in Charge, Contagious Unit, Grady Memorial Hospital, Atlanta, Ga.

BEN FRIEDMAN, B.S., M.D.

Associate Professor of Medicine, Southwestern Medical School of the University of Texas, Dallas, Texas.

W. ELIZABETH GAMBRELL, B.A., M.S., PH.D., M.D., M.P.H.

Instructor in Medicine, Emory University School of Medicine, Atlanta, Ga.

T. R. HARRISON, B.A., M.D.

Professor of Medicine, Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas, Texas.

## CONTRIBUTORS

**HANS H. HECHT, M.D.**

Associate Professor of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

**ALBERT HEYMAN, B.S., M.D.**

Associate in Medicine, Emory University School of Medicine; Attending Physician, Director, Clinic for Genitoinfectious Diseases, Grady Memorial Hospital; Public Health Physician, Georgia Department of Public Health, Atlanta, Ga.

**B. V. JAGER, B.A., M.D.**

Associate Professor of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

**WILLIAM M. M. KIRBY, B.S., M.D.**

Associate Professor of Medicine, University of Washington School of Medicine, Seattle, Wash.

**DANIEL HARVEY LABBY, B.A., M.D.**

Assistant Clinical Professor of Medicine, University of Oregon School of Medicine, Portland, Ore.

**GLEN R. LEYMASTER, B.S., M.D., M.P.H.**

Associate Professor of Public Health and Preventive Medicine, Assistant Professor of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

**THOMAS E. MACHELLA, B.A., M.D.**

Assistant Professor of Medicine and Associate in Physiology, University of Pennsylvania School of Medicine; Chief, Gastrointestinal Section of the Medical Clinic of the Hospital of the University of Pennsylvania, Philadelphia, Pa.

**D. S. MARTIN, B.A., M.D., M.P.H.**

Professor of Microbiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

**M. F. MASON, B.S., PH.D.**

Professor of Pathological Chemistry, Department of Medicine, Southwestern Medical School of the University of Texas; Chemist, Parkland Hospital, Dallas, Texas.

**H. HOUSTON MERRITT, B.A., M.D., M.A. (HON.)**

Professor of Neurology, College of Physicians and Surgeons, Columbia University; Director of the Neurological Services, Neurological Institute, Presbyterian Hospital, New York City, N. Y.

**MAX MICHAEL, JR., B.S., M.D.**

Assistant Professor of Clinical Medicine, Emory University School of Medicine, Atlanta, Ga.; Chief of Medical Service, Lawson Veterans Administration Hospital, Chamblee, Ga.

**EDWARD S. MILLER, M.D.**

Instructor in Medicine, University of Colorado School of Medicine, Denver, Colo.

**C. A. MOYER, B.A., M.S., M.D.**

Professor of Surgery, Southwestern Medical School of the University of Texas, Dallas, Texas.

**GEORGE PICKERING, M.A., M.D., F.R.C.P.**

Professor of Medicine, St. Mary's Hospital Medical School, University of London, London, England.

**CHARLES H. RAMMELKAMP, B.A., M.D.**

Associate Professor of Preventive Medicine, Assistant Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio; Field Director, Streptococcal Disease Laboratory, Francis E. Warren Air Base, Wyoming.

**J. C. RANSMEIER, B.A., M.D.**

Instructor in Medicine, Emory University School of Medicine, Atlanta, Ga.; Medical Service, Lawson Veterans Administration Hospital, Chamblee, Ga.

**EDWARD C. REIFENSTEIN, JR., B.A., M.D.**

Research Associate, Sloan-Kettering Institute, Memorial Cancer Center; Executive Director, Medical and Research Division, Ayerst, McKenna & Harrison Limited, New York City, N. Y.

**WILLIAM H. RESNIK, PH.B., M.D.**

Stamford, Conn.

**ARTHUR P. RICHARDSON, B.A., M.D.**

Professor and Chairman, Department of Pharmacology, Emory University School of Medicine, Atlanta, Ga.

**DANIEL SCIARRA, B.A., M.D.**

Instructor in Neurology, College of Physicians and Surgeons, Columbia University, New York City, N. Y.

**T. F. SELLERS, M.Sc., M.D.**

Director, Georgia Department of Public Health, Atlanta, Ga.

**ANDREW B. SMALL, B.S., M.D.**

Clinical Assistant Professor of Surgery, Southwestern Medical School of the University of Texas; Attending Surgeon, Baylor University and Parkland Hospitals, Dallas, Texas.

**WESLEY W. SPINK, B.A., M.D.**

Professor of Medicine, University of Minnesota Hospitals and Medical School, Minneapolis, Minn.

**EUGENE A. STEAD, JR., B.S., M.D.**

Professor and Chairman, Department of Medicine, Duke University School of Medicine; Physician-in-chief, Duke Hospital, Durham, N. C.

**E. STRAUSS, B.S., M.D.**

Assistant Professor of Preventive Medicine, Southwestern Medical School of the University of Texas, Dallas, Texas.

**GEORGE W. THORN, M.D., M.A. (HON.)**

Hersey Professor of the Theory and Practice of Physic, Harvard University Medical School; Physician-in-chief, Peter Bent Brigham Hospital, Boston, Mass.

**FRANK H. TYLER, B.A., M.D.**

Assistant Research Professor of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

**SHIELDS WARREN, M.D., Sc.D.**

Director, Division of Biology and Medicine, United States Atomic Energy Commission, Washington, D. C.

**PAUL C. WILLIAMS, B.A., M.D.**

Associate Professor of Orthopedic Surgery, Southwestern Medical School of the University of Texas, Dallas, Texas.

**M. M. WINTROBE, B.A., B.S., M.D., PH.D.**

Professor and Head, Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

**LOWELL A. WOODBURY, B.S., M.S., PH.D.**

Assistant Professor of Physiology, University of Utah College of Medicine, Salt Lake City, Utah.

**C. P. YAGLOU, B.S., M.S., M.A. (HON.)**

Professor of Industrial Hygiene, Harvard University School of Public Health, Boston, Mass.



## Preface

The aim of this book is to present within the confines of a single volume a consideration of the disorders that comprise the province of internal medicine. An attempt has been made to integrate the pertinent content of the preclinical sciences with clinical medicine, and to approach the subject not only from the standpoint of disorders of structure, but also by way of abnormal physiology, chemistry, and disturbed psychology. This method of presentation follows the modern trend in medical education. The book is directed primarily at the student and physician who desire a presentation of the important scientific principles that are necessary for a rational understanding of the development, evolution, and management of internal diseases.

The modern view of clinical teaching holds that the classic approach, with primary emphasis on specific diseases, is inadequate, and that the student or practitioner cannot be expected to recognize disease in its various manifestations and to manage it intelligently unless he also understands the basic mechanisms of its cardinal manifestations. The basic mechanisms of disease are no longer solely of academic interest to the investigator and to the teacher, but have now become of immediate practical importance in the care of patients.

Since a proper attitude toward the patient is fundamental to medical practice, the book begins with an introduction entitled Approach to the Patient. This chapter is the work of Drs. William Dock and Henry Brosin, and the editors. The functional approach to the principles of internal medicine is covered in the first five parts of the book. The last two parts deal with specific infectious diseases, and diseases of organ systems.

Part I, Cardinal Manifestations of Disease, includes discussions of the major symptoms and signs; and the manifestations of circulatory failure, renal failure, and anemia, as well as the mechanisms whereby these develop.

Part II, Physiologic Considerations, deals with certain principles which are especially germane

to internal medicine. In planning this portion of the book, the question has repeatedly arisen as to whether certain highly technical subjects should be included. Even though some of these subjects seem at first to be far removed from the bedside, second thought reveals that they are already essential for the understanding of certain disease processes. They will be of increasing importance in the future. The chapter dealing with principles of intermediary metabolism is an example. Initially, this chapter was designed to afford a basis for a proper approach to the subject of diabetes, certain other endocrine disorders, and the deficiency diseases. For these purposes a brief summary of the final common metabolic pathway, including electron transfers, seemed necessary, even though such a consideration involved excursions into organic chemistry, and might be considered as too theoretic. Advances in research soon made it apparent that, for example, the mode of action of diphtheria toxin could be understood only if the role of the cytochrome system in electron transfer were comprehended. The theory of today, when sound, becomes the practice of tomorrow.

Certain manifestations of disease, such as fever and alterations in leukocytes, are considered in Part III, Reactions to Stress and to Antigenic Substances, because recent evidence suggests that psychic disturbances, immunochemical disorders, and the usual physical stresses may act through closely allied mechanisms.

Part IV, Metabolic and Endocrine Disorders, also covers the nutritional disturbances. The omission of the chapters on muscle and bone from Part VII, which deals with diseases of the organ systems, and the inclusion of discussions of metabolic disorders of bone and muscle in this portion of the book, is a departure from custom. It is believed that this arrangement is justified, since expanding knowledge has placed most of the important nonsurgical disorders of bone and muscle in the metabolic field.

Parts V and VI deal with Disorders Due to

## PREFACE

Chemical and Physical Agents, and Diseases Due to Biologic Agents. Part V includes brief discussions of radiation injury and of the medical aspects of atomic explosions. Repetition has been avoided in Part VI by the inclusion of chapters dealing with the general management of infectious diseases, and with the use of antibiotics.

Part VII, Diseases of Organ Systems, concludes the book. The unconventional arrangement of the chapters dealing with diseases of the heart is explained in a foreword. In the section on diseases of the nervous system, the discussion has been centered on the common neurologic problems.

The bibliographies are brief and are not intended to be comprehensive. In general, they are limited to only a few especially important original papers, to reviews and monographs containing in themselves extensive references, and to more recent publications.

The decision to devote a considerable part of the book to considerations of basic principles has made it possible to condense many parts of the book, through elimination of needless repetition under each specific disease. Rare disorders have been treated summarily by a few lines or by tabulation, or have been omitted entirely. As the volume has progressed, the conviction has grown that what the student and the physician need is thorough familiarity with common disorders, plus understanding of basic principles.

The book is not the work of the editors and authors alone. A large number of individuals of varying background and experience have performed invaluable service as critics. Among those who have been given most generously of their time for this purpose are Drs. B. V. Jager, Hans H. Hecht, John F. Waldo, Frank H. Tyler, Glen R. Leymaster, G. E. Cartwright, J. C. Nunemaker, Harold Brown, Emil S. Smith, and Francis Binkley of Salt Lake City; Drs. Arthur J. Merrill, Philip Kramer Bondy, Robert P. Grant, James V. Warren, J. C. Ransmeier, Walter H. Sheldon, Walter L. Bloom, Charles M. Huguley, and John L. Patterson, Jr., of Atlanta; Drs. Peter H. Forsham, Thomas F. Frawley, S. Richardson Hill, Jr., Marcel Roche,

and D. Laurence Wilson of Boston; Drs. Julian Acker, E. Strauss, Ben Friedman, M. F. Mason, Willis Sensenbach, Howard E. Heyer, and Louis Tobian of Dallas. Selected portions of the book have been criticized by Drs. George Burch, William Cromartie, William Dock, Thomas Farmer, James Gill, Louis Katz, Eugene Landis, Isaac Starr, and Edward Sulkin. To all these, and many others, including members of our resident staffs and some of our medical students, we are deeply grateful.

Since all chapters have been revised at least once and some several times, and since each revision has been sent to each member of the editorial group, the secretarial work has been unusually demanding. Among those who have contributed importantly are Mrs. Leane Bronstad, Miss Janice Reiter Craig, Miss Betty Anne Finnell, Mrs. Rita Hurley Guinessy, Mrs. Judith Hopkins, Miss Mary Ruddock Hyde, Mrs. Marian Nelson, Miss Betty Pharr, Miss Rita Purdy, Mrs. Ora Runyon, Mrs. Marie Starks, and Miss Alida Woolley.

The customary polite reference would not do justice to the members of the staff of the Blakiston Company, who have constantly coöperated in every possible way. Special thanks is due Mrs. Eunice Stevens, Associate Medical Editor. Miss Minnie Mae Tims, long-time secretary to the Editor-in-Chief, and Mrs. Stevens have given the major part of five years to the task. Their performance has been far above and beyond the call of duty.

The usual acknowledgment to the publisher would not express our attitude toward the Vice President of the Blakiston Company, Mr. T. A. Phillips, whose concern for the scientific quality of the book has equaled our own. The association with him has been a source of genuine pleasure.

May 1950

P. B. B.  
T. R. H.  
W. H. R.  
G. W. T.  
M. M. W.

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*Editor:* PAUL B. BEESON

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## Introduction

# Approach to the Patient

No greater opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering he needs technical skill, scientific knowledge, and human understanding. He who uses these with courage, with humility, and with wisdom will provide a unique service for his fellow man, and will build an enduring edifice of character within himself. The physician should ask of his destiny no more than this; he should be content with no less.

In the practice of medicine the physician employs a discipline which seeks to utilize scientific methods and principles in the solution of its problems, but it is one which, in the end, remains an art. It is an art in the sense that rarely, if ever, can the individual patient be considered the equivalent of an experiment so completely controlled that it is possible to exclude judgment and experience from the interpretation of the patient's reactions. It is an art, too, in the sense that the practicing physician can never be content with the sole aim of endeavoring to clarify the laws of nature; he cannot proceed in his labors with the cool detachment of the scientist whose aim is the winning of the truth, and who, theoretically, is disinterested in the practical outcome of his work. The practicing physician must never forget that his primary and traditional objectives are utilitarian—the prevention and cure of disease and the relief of suffering, whether of body or mind.

Today, with periodic health, pre-employment, and insurance examinations, the scope of the physician has been enlarged. He must be accomplished in the study of presumably well people in addition to those who are ill. With the latter group the history is of great value; with those who are well, objective methods of study are all-important, for patients tend to emphasize dif-

ferent facts, depending on whether they seek employment, pensions, disability, or insurance. It is obvious that the same symptoms will rarely be described in the same way by the soldier desiring release from military duty, by the prospective employee seeking certification of his fitness for work, or by the patient who is alarmed because of fear of a serious ailment. The approach to the patient, therefore, must be varied to correspond with the conditions which bring physician and patient together. Yet there are fundamental considerations which underlie all sound practice.

In every case the physician must have in mind three responsibilities. First, comes the search for the underlying causes of all symptoms noted by the patient or his family, and the cure or alleviation of the disorder producing these symptoms. Next, comes the detection of latent disease or of potential sources of disability, and the acquainting of the patient with steps to be taken in order to maintain his health and to protect others if his illness is communicable. Finally, the physician must understand and evaluate the environmental stresses and the patient's probable reaction to them. All of these are of immediate concern in those who are not acutely ill or in people sent for examination by insurers or employers. In those confined to bed the latter two responsibilities become urgent only on convalescence, save when contagion, or the occupational or psychogenic origin of diseases, is demonstrable. The approach to the patient, therefore, begins by determining what the urgent, immediate issues are, and what can properly be studied more effectively at a later date.

Since intelligent treatment depends primarily on a knowledge of the cause, diagnosis becomes the foundation on which the art of medical practice rests. Diagnosis implies the discovery of all the various factors that are responsible for the illness. It involves an estimation of the extent

## INTRODUCTION

and severity of the functional and anatomic changes produced by the disorder and it necessitates an insight into the rate of progress and the probable outcome. To this end are correlated and integrated the facts obtained from the history, the physical examination, and the laboratory investigations.

### HISTORY

The history aims to embody all the facts that may have influenced the patient in a medical way up to the time he consults the physician. Most important of all, in the case of the patient who is ill, the history contains an account of the symptoms that have impelled him to seek advice. The history can never be the mere mechanical recording of data. Each statement must be scrutinized for its possible bearing on the present status of the patient, and, more particularly, for any light it may throw on the symptoms of which he now complains. The mind of the physician must be constantly alert to the possibility that any event related by the patient, any symptom, however trivial or remote, may yet hold the key to the solution of a medical problem. In the main, we are dealing with subjective manifestations filtered through the consciousness of individuals who vary in their capacity to observe and describe; who differ widely in their responses to the same stimuli; whose accounts are colored, consciously or unconsciously, by fears and misconceptions as to the nature and significance of their disorders. Added to these difficulties, one occasionally encounters the barrier of language, so that it is not surprising if even the careful physician becomes somewhat impatient with the arduous task of collecting data that cannot be accurately weighed or measured, but that have value only in so far as they can be considered to represent more or less close approximations of the truth.

Despite these shortcomings, the taking of the history, by and large, constitutes the most important part of the examination. A skillfully taken history, carefully interpreted, will provide important information regarding the emotional and psychologic background of the patient which may be of utmost value in the solution of his problem. At the same time an interested sympathetic interview constitutes the foundation for a successful patient-physician relationship.

It is the subjective symptom that usually calls

the attention of the patient to his departure from good health; for him, that is sufficient reason that the meaning of the symptom be thoroughly explored. It is the symptom that determines the physician's line of inquiry to the end that from the various possible causes for the symptom there will emerge a pattern or clinical picture that will permit the physician to draw at least a tentative conclusion as to the nature of the malady. In some instances so clear a picture will be drawn, as when a classic story of angina pectoris is obtained, that the diagnosis may be largely established from the symptoms alone, regardless of the outcome of the physical and laboratory examinations. In most cases the history will not be so decisive, but it will have so limited the diagnostic possibilities that a logical program of investigation will be suggested. It is usually from the history that one can estimate most accurately the speed and evolution of the disease. It is in the taking of the history and in the analysis and interpretation of the data contained therein that the skill, knowledge, and experience of the physician are most frequently and rigorously tested.

Because the symptom is a subjective manifestation, one that is not readily corroborated or measured, there is too often a disposition to value it lightly, or even to disregard it when it cannot be explained on the basis of our present-day knowledge. Credulity is to be avoided; but only less zealously must one steer away from an attitude of such rigid skepticism that one refuses to entertain the possibility that a core of truth may be contained in an odd or unfamiliar phenomenon described by the patient. The demonstration that the virtue of cod liver oil was something more than an old wives' fancy, and the discovery of the leaf of the foxglove as a therapeutic agent in heart failure, may be cited as examples of the beneficent effect of listening with an open mind. "Disease often tells its secrets in a casual parenthesis."

### PHYSICAL EXAMINATION

Little need be said regarding the importance of the physical examination, for early in his training the physician becomes impressed with the diagnostic value of physical signs, objective and verifiable evidence of pathologic change. Regardless of the confusion of data obtained from the history, regardless of the inconsistencies of statement voiced by the patient, the physical sign has an indisputable value as solid evidence

in the case. Symptoms and signs have varying clinical value in proportion to the extent to which they narrow the field of possible diagnosis. From this point of view, the value of physical signs is beyond question. Skill in physical diagnosis is acquired with experience. But it is not experience merely in the technic of physical examination that determines how successful one may be in eliciting the signs that provide the clues to the correct diagnosis. Detection of a few scattered petechiae or of a faint diastolic murmur or of a small mass in the abdomen is not accomplished because the trained clinician has eyes, ears, or fingers that are more acute than those of his colleagues. Usually these diagnostic signs have been revealed because the observer has been prepared by other features of the history or examination to search for them.

All investigations of the body should be regarded as part of the physical examination. The use of various instruments such as the ophthalmoscope, sphygmomanometer, galvanometer, or roentgen tube may be necessary to study certain structures and functions of the patient, but all these methods of study are part of the physical examination, and all of them may be used by physicians practicing internal medicine. Tests made on fluids or tissues removed from the patient are laboratory examinations, and, since it is so obvious that it is too often forgotten, it should be stated that the proper collection of material is as important as its correct study.

### INSTRUMENTAL AND LABORATORY EXAMINATIONS

The last century has witnessed the introduction of newer methods of instrumental and laboratory investigation of ever-increasing precision and refinement, and inevitably there has been a drift toward reliance on knowledge gained from these special means of study in the solution of clinical problems. No one can view the enormous advances that have been made in these past several decades without recognizing that they have come from the use of technics of exactitude that were unavailable in earlier times. These newer methods of examination should be accepted with gratitude; yet one hears, from time to time, lamentations regarding the neglect that is accorded the older traditional sources of information gained from the history and the use of the unaided senses. But what force can these lamen-

tations have when it has been so abundantly demonstrated that roentgenologic inspection of the chest will reveal changes that are completely beyond the perceptions of even the most skilled exponent of the art of physical diagnosis; when similar methods of examination of the digestive tract uncover with certainty what may only dimly be surmised from the history and the routine physical examination; when differentiation of many infectious diseases can be placed on a sure footing only by exact bacteriologic and immunologic technic; and when only by more or less intricate methods of chemical analysis can diseases of metabolism be studied? The need is neither to stress the value nor to deplore the use of these special methods of examination; rather is it to recognize their limitations and their proper use in the practice of medicine. By virtue of their impersonal quality and the complexity of the technics involved in obtaining them, data secured by instrumental and laboratory methods are frequently surrounded by an aura of authority, without heed to the fact that the data are collected by fallible human beings who are capable of committing errors of technic, or who may misinterpret the most precise evidence. Too great emphasis may be placed on minor deviations that may yet lie well within the range of normality. These and other possible errors serve to indicate that even these data cannot release the physician from the necessity of careful observation and study of the patient. The wise physician is he who understands the merits and limitations of each source of information, whether it be derived from the history, or the physical examination, or the laboratory investigations. Barring those exigencies that make careful study impracticable or impossible, the history and physical examination should be thorough and painstaking, and the special examinations and laboratory tests should be adequate to furnish what additional information may be necessary to give a completeness that is appropriate to the circumstances. In some cases it will suffice to use merely the simple tests that should be at the disposal of every practicing physician; in the more obscure cases the full resources of the most advanced teaching hospital may be essential for the successful unraveling of the clinical problem.

Despite the constantly increasing application of scientific methods to the problems of medicine,

## INTRODUCTION

there remain large areas that are as yet insusceptible of solution by the use of precise methods. To extract the telltale clue from a maze of confusing symptoms, to determine from a mass of conflicting physical signs and laboratory data the ones that are of crucial significance, to know in a borderline case when to initiate and when to refrain from a line of treatment—these decisions are not usually the outcome of laboratory study alone. In the end, these decisions are expressions of judgment acquired through “assimilated experience.” The skill with which he meets such perplexing problems defines, in large measure, the ability of the physician as a practitioner of the art of medicine in the field of organic disease. But the art of medicine is not confined to organic disease; it deals also with the mind of the patient and with his behavior as a thinking, feeling human being.

### THE PATIENT AS A PERSON

The student receives much expert coaching in the methods of physical and laboratory diagnosis, and it is in these areas that he will most easily develop the skills which permit him to be comfortable with the patient. Mastery of the more intangible psychologic aspects of medicine is not so easily learned, however. The skills essential here depend not simply on instruction but on emotional maturity, manifested by sensitive self-cultivation of the ability to see deeply and accurately the problems of another human being. The challenge is further magnified by the fact that the examining physician is himself a human instrument, subject to error due to the events in his own biography.

Just as the physical growth of the organism depends on an adequate and balanced supply of appropriate foodstuffs, so does emotional growth depend upon receiving the proper psychologic nutrients. Although each organism is born with manifold potentialities determined by his genes, the emotional climate nourishing him will shape his eventual character and abilities just as surely as foodstuffs will modify his physique. Emotions possess the capacity to exert force and thereby alter behavior, including the biochemical processes of the body, no less than invading bacteria or foreign bodies.

It is not easy to keep these basic facts in mind when examining a draped patient in the relatively neutral domain of the hospital ward or

even in the private examining room. There are potent obstacles that stand in the way of the physician's making an adequate study of the patient's emotional life. Organic lesions have a way of compelling attention to themselves, and it is less exhausting to limit one's focus to the sphere of organic disease. More time, energy, and experience are necessary to view the patient as an active participant in an enormous moving pageant which includes the personal eccentricities of his forebears as well as the hopes for his children's future. It is not enough to know that poverty, insecurity, and perhaps poor vocational and domestic relations are now keeping the patient unhappily depressed, for all too often it is apparent that present socioeconomic (external) factors are not crucial determinants in the contemporary scene. To explain the phenomena, it is necessary to remember that past experiences of each individual from earliest days are not altogether forgotten but are the foundations of our current system of meeting our daily problems. Under pressure some of our defensive attitudes, which were useful in infancy and childhood but inappropriate in adult life, have a way of returning to the scene of action; one of the oldest, the state of readiness for fight or flight (Cannon), may be a precipitating cause of illnesses such as peptic ulcer or hypertension when called upon too frequently.

The physician has a special function in society because he should be a trained biologist in human behavior as well as in human diseases. He brings highly technical knowledge and skills to bear upon the problems of his patient as a person as well as upon the patient's physiologic functioning. He should bring to the suffering patient a quiet humanity, a confidence and security based upon the conviction that all will be done that can be done. The patient must feel that his unique individuality is recognized and appreciated and that his life's problems are meaningful. This is important in patients with well-defined organic disease as well as in the “stress” syndromes largely due to emotional pressures expressed through the body. If we can accept the principle of causality in human behavior we can, with patience and diligence, learn to fathom the large outlines of a person's motivations even though the details remain obscure.

In clinical medicine it is common practice to think of disease in terms of “organic” and “func-

tional," and to imply by the latter expression a disturbance due solely to emotional instability or nervous strain. It is recognized, of course, that there are a vast number of bodily derangements which are due to functional dislocations that often are based neither on structural disease nor on primary psychogenic disorder: shock due to extracellular fluid deficit, diabetic ketosis and paroxysmal auricular tachycardia are examples. There are other less dramatic forms of nonpsychogenic functional disturbances that so frequently resemble malfunctions due to psychic influence, and that often are so intricately woven with emotional components that it may be forgotten that other factors may be playing an important or even predominant role. A palpitation that is clearly not due to organic disease and that may readily be attributed to "nerves" may actually be due to hypoglycemia brought on by faulty diet. Chronic indigestion or diarrhea or recurrent headache may be ascribed to emotional disturbance when exhaustive investigation has revealed no structural disorder or other tangible basis for the ailment; yet a specific intolerance to foods may turn out to be the chief cause of the trouble. Statements so trite in theory would hardly deserve mention, were they not so often forgotten in practice.

### MANAGEMENT OF THE PATIENT

The art of medicine lies in establishing *all* the diagnoses in each case, and in instituting the most effective management, even though absolute accuracy of diagnosis of many conditions is often impossible. The restoration of the patient's comfort and confidence should begin with his initial contact with the physician and his assist-

ants. Gentle, thorough, and interested interrogation and examination prepare the way for more painful procedures that may be essential. Even the patients who experience relief from the propitiatory nature of suffering, expect and need consideration and humane, affectionate care from their families, their physicians, and their nurses or other attendants. There must, however, be firmness in obtaining coöperation in study and management, both of which should be carried out with minimum discomfort or risk to the patient. Disease often profoundly alters personality and makes skill in handling the patient as important as familiarity with diagnostic procedures, and the nature, seats, and causes of disease. "The attitude of the patient approaching his doctor must always be tinged—for the most part, unconsciously—with distaste and dread. Do not let yourselves believe that however smoothly concealed by education, by reason, and by confidential frankness these strong elements may be, they are ever in any circumstances altogether absent" (Wilfred Trotter).

Tact, sympathy, and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs, and disturbed emotions. He is human, fearful, and hopeful, seeking relief, help, and reassurance. To the physician, as to the anthropologist, nothing human is strange or repulsive. The misanthrope may become a smart diagnostician of organic disease, but he can scarcely hope to succeed as a physician. The true physician has a Shakespearean breadth of interest in the wise and the foolish, the proud and the humble, the stoic hero and the whining rogue. He cares for people.



## Part I

# CARDINAL MANIFESTATIONS OF DISEASE

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1

## General Considerations of Pain

Eugene A. Stead, Jr.

### Pain Perception and Reaction to Pain

Nerve Pathways  
Pain-Sensitive Structures  
Quality of Pain  
Double Response from the Skin  
Hyperalgesia of Skin  
Referred Pain  
Central Nervous System

**Pain Perception and Reaction to Pain.** The nerve structures transmitting pain are different from those conducting cold, heat, touch, and pressure. The threshold for perception of pain is defined as the lowest intensity of stimulus which is recognized as pain. It is approximately the same in all normal subjects. While the perception of pain shows little variation, the threshold at which the subject reacts to the pain varies widely. Emotionally disturbed patients in general show a lower threshold for reaction than do normal subjects. Included in the reaction to pain are not only the voluntary reactions but also those mediated through the autonomic nervous system, as tachycardia, sweating, changes in intestinal activity, and rise in arterial pressure. The reaction of the person to pain depends in part on the meaning of the sensation interpreted in the light of past experiences. Conditioned reflex involving the highest cerebral connections may be important. The importance of higher centers in the over-all reaction to pain is well illustrated by studies on patients with bilateral frontal lobotomy or topectomy. Following these operations, in which pathways from the frontal lobe to the thalamus are interrupted, one observes a dissociation between painful stimuli and the interpretation of pain. This fact illustrates that the accompanying pain has a large emotional as well as a purely physical component.

**Nerve Pathways.** Bright pricking pain is carried in thick, rapidly conducting myelinated fibers. Burning pain from the skin is carried by slower conducting fibers of a small size. Visceral pain is transmitted by myelinated and non-

myelinated fibers which pass through the sympathetic chain. The cell bodies of the sensory nerves, including those passing through the sympathetic chain, are located in the posterior root ganglions. These connect with a second neuron whose cell body is in the posterior horn. Pain impulses cross promptly to the opposite side of the cord and ascend in the lateral spinothalamic tract to the thalamus, where additional neurons extend to the postcentral area of the cerebral cortex.

**Pain-Sensitive Structures.** Pain arises from many structures. A stimulus which causes pain in the skin may not produce pain in the intestine or mesentery. Many organs known to be pain-sensitive were once called insensitive because they did not give rise to pain when cut.

The pain response of the skin is common knowledge. Although the subcutaneous fat gives rise to little pain when pierced by a needle or cut, pain is present if cutaneous nerves passing through the fat are injured. Deep fascia is painful to needle puncture. In the muscles the pain response to needle puncture or cutting is slight, but is severe when provoked by the injection of hypertonic solutions or by ischemia from vascular disease. Muscles produce pain when in spasm, as in tetany or night cramps. Tendons and periosteum are sensitive to pinprick or hypertonic solutions. Pain is a prominent sign in periostitis. The dentine and deeper structures of the teeth are pain-sensitive. Compact bone may be cut without pain, but pain may come from cancellous bone. Joints are insensitive to needle point, knife, or cautery, but the synovial membrane is sensitive to scratching, hypertonic saline, and inflammation. Arteries and veins—more often arteries—may react painfully to needle puncture. Distortion of cranial vessels by traction, displacement, or distention is a common cause of headache.

Pain from the heart is produced by ischemia. The sensory fibers pass through the sympathetic chains and enter the cord in the upper five thoracic roots. The parietal pleura and diaphragmatic surface of the parietal pericardium, which are pain-sensitive, are supplied by the intercostal and phrenic nerves. Pain fibers to the parietal peritoneum run in the intercostal nerves. Pain in the gastrointestinal tract is produced by local trauma of an engorged or inflamed mucosa, distention or spasm of intestinal muscles, and traction upon mesenteric attachment. The nerve fibers pass through the sympathetic chain to enter the spinal cord in the lower thoracic segments. Renal and ureteral pain passes through the lower splanchnic trunks and lower thoracic and first lumbar segments. From the trigone and structures below the bladder, pain impulses pass to the cord through the sacral parasympathetic rami. Stimuli from the body of the uterus pass to the cord from the tenth thoracic to the first lumbar spinal segment by way of the superior hypogastric plexus; from the cervix by the second, third, and fourth sacral nerves.

**Quality of Pain.** Pain from the skin is accurately localized and, in carefully controlled experiments, has the same quality regardless of whether the stimulus is pricking, pinching, pulling hair, burning, electric current, or application of irritant poisons. In addition to the immediate pain produced by injury, pain occurs as an after-effect of injury to the skin. The intensity varies, but the quality is the same regardless of the stimulus producing the injury. Direct stimulation of the cutaneous nerves leads to the same type of pain as arises from the skin.

The quality of pain from the deeper tissues differs from that of skin pain. It is more diffuse and long lasting, and may radiate. It is more apt to be associated with nausea, slowing of the pulse, and fall in blood pressure.

**Double Response from the Skin.** Lewis has described two immediate painful responses from stimulation of normal skin. At the toe, the second response occurs approximately two seconds after the first. He interprets this as resulting from conduction of pain by fibers of different size with different rates of conduction. The fast conduction is about 20 times more rapid than the slow. Only the delayed response is present when the fingers become numb from marked

asphyxia. Patients with tabes dorsalis may show a delayed reaction to pinprick because of the destruction of the faster fibers. In the deeper structures, pain comes on more slowly and lasts longer, and no double response is observed.

**Hyperalgesia of Skin.** The skin may become abnormally sensitive to stimuli because of (1) lowering of pain threshold, and (2) alterations in excitability of central pain pathways supplying skin so that various stimuli evoke a more intense and persistent sensation. Inflammations cause a sharp fall in pain threshold not only in the skin but also in the mucous membranes of the nose, stomach, colon, bladder, and esophagus. In the second type of hyperalgesia, the pain threshold is not lowered but stimuli exceeding the threshold are felt with greater intensity. This is the type of hyperalgesia sometimes associated with referred pain.

**Referred Pain.** While pain from the skin is well localized, pain from deep-lying structures may be referred remotely. This is true of deep-lying somatic structures as well as visceral organs. The distribution is in part segmental; it may fill only part of a segment, yet "overflow" into adjacent segments. If the deep structures producing the pain and the nerve roots supplying the area of referred pain are known, then one also knows the nerve roots through which the sensory fibers from the deep diseased structures enter the cord. The pain of angina pectoris frequently radiates down the inner surface of the left arm in the area supplied by the eighth cervical and first thoracic spinal segments. This suggests that some of the sensory nerves from the heart which travel in the sympathetic trunk establish central synaptic connections at these cord levels. Pain from the hip joint, which is referred to the knee, and pain from the spine or muscles of the back, which is referred to the extremities, are other examples of segmental distribution. The referred pain is frequently accompanied by hyperalgesia of the skin.

The simplest explanation for referred pain is that suggested by Lewis:

If we suppose that certain tissues are represented in great detail in the sensorium, we can also understand that pain arising in these tissues may be localized with accuracy. But in other tissues having only a massive central representation, localization may be expected to be less accurate. Segmental reference of deep pain may mean no more than that, centrally, the deep tissues supplied by a given cord segment have a gen-

eral, but little detailed, representation. Thus, the impulses received, whether these are derived from a viscous or from deep somatic tissue, would tend to awaken very similar sensory impressions and to be localized over a general sphere or spheres having no very precise margins. And it may be regarded as natural enough that the general reference should be to regions that are relatively superficial, regions from which we are habitually receiving sensory impressions, and which are endowed with some positional sense.

This is an adequate explanation of referred pain which is not accompanied by hyperalgesia. Injection of procaine into the superficial or deep areas of referred pain does not affect the pain. In certain instances, referred pain is accompanied by superficial or deep hyperalgesia, and the referred pain is decreased by injection of procaine into the hyperalgesic areas. It would appear that stimuli normally not causing pain may do so if a segment of cord is sufficiently excited by visceral or other stimuli. At times,

stimuli from deep structures may cause spasm in skeletal muscles adjacent to or distant from the primary source of the pain. The spasm may become very painful, and injection of procaine into the muscle will relieve it.

**Central Nervous System.** Lesions of the thalamus produce spontaneous pain, hyperalgesia, and painful overreaction to slight stimuli. The excessive response to effective stimuli is believed to result not from irritation but from the removal of control by destruction of fibers connecting the cortex and the thalamus.

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# 2

## Headache

George Pickering

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### INTRODUCTION

Interpreted literally, headache signifies ache or pain located anywhere in the head; but its meaning has been narrowed by long usage to signify ache or pain experienced in the region of the cranial vault.

Headache is thus an experience or sensation which can be described. As in other forms of pain,

its description can be analyzed into certain components—namely, quality, location, intensity, time relations, and the manner in which it is influenced by other events in the immediate environment of the patient. These characteristics, the associated sensations, and the presence of certain objective phenomena or physical signs are the means whereby it is possible to recognize, clinically, which of the known kinds of disorder is responsible for headache in a given instance. The characteristics of headache may now be discussed briefly in general terms.

**Quality.** The quality of pain is often described in terms of past experience, actual or imagined. Such descriptions are of limited value in deciding the origin of pain. There is strong evidence for the belief that if associated sensations are excluded, the subject can recognize only two types of pain by its quality: superficial pain arising from the

skin, which is sharp and burning in character; and deep pain arising from all structures deep to the skin, which is dull or aching. With very few exceptions, headache is a dull, aching pain, and thus of the type that arises from structures deep to the skin.

**Location.** Pain arising from the skin is localized fairly precisely to its point of origin. Pain arising from structures deep to the skin is less accurately localized the farther the point of origin is beneath the surface, and both pain arising from really deep somatic structures and pain from visceral tissues are referred in a segmental pattern. These same principles apply to headache. Thus pain arising from a localized lesion not far beneath the surface, such as temporal arteritis, may be fairly well localized over the lesion itself. But with deep extracranial lesions, such as those affecting the accessory sinuses of the nose and the upper cervical vertebrae and their joints and ligaments, pain may be more widely referred in an area that is not directly over the lesion; still more so is this true of intracranial lesions. Although headache is not necessarily located directly over the lesion, the reference of pain arising from the various structures from which it may arise is fairly constant from one subject to another, and is thus of some diagnostic value.

**Intensity.** The intensity of pain is notoriously hard to assess. Patients' statements on intensity are not of themselves of much value, for it is not unusual to find that the most extravagant epithets are applied to pains for which there is little organic basis, and where the physician is forced to conclude that the major disturbance is not of the body but of the mind. The sensitivity to pain varies with different individuals, and with the same individual under different circumstances. Intensity may be judged by other criteria. Thus headache which wakens the patient at night, and, to a lesser extent, headache which prevents sleep, are nearly always of organic origin. Severe headaches again are often accompanied by vomiting, but this is more common in those of intracranial than of extracranial origin. The severest headaches are probably those associated with meningitis, and here the patient may frequently sweat with the pain, and be obliged to cry out.

**Time-Intensity Curve.** Very rarely is headache a momentary flash of severe pain, and then usually it is due to trigeminal neuralgia affecting the supraorbital division of the nerve. More usu-

ally the pain lasts minutes or hours, and the duration of pain may be of assistance, diagnostically. Thus in cerebral tumor the pain occurs at first in short paroxysms. In many forms of headache of extracranial origin and of little pathologic import, the pain may at the outset last for some days. Some pains, though continuous, wax and wane with the pulse beat, and it is clear that in such instances of "throbbing" pain the pain arises from a structure which is moved by the arterial pulse.

**Relationship of Headache to Other Events in the Environment.** In many instances of organic headache, the tissue disturbance which leads to the excitation of the pain nerves is influenced by events in the environment. Thus exposure to cold may act as a trigger to that ill-defined process that will be considered under nodular or fibrotic headache. In cerebral tumor, circumstances influencing the inflow or outflow of blood from the cranial cavity may precipitate headache. The headache of hypertensive disease is most frequent on waking in the morning, and that of infection of the nasal accessory sinuses may recur at certain hours of the day with almost astonomic regularity. Other examples will be found later, but these instances serve to show that an analysis of this feature of headache is of considerable value from the diagnostic aspect, and the facts so elicited must, of course, be accounted for in any hypothesis that seeks to explain the mechanism of pain.

**Pain-Sensitive Structures.** The structures which may give rise to headache are, in general, those of the cranial cavity, the cranium itself, the covering of the skull, and other adjacent structures such as the orbital contents, the accessory nasal sinuses, and the deep structures of the neck close to the occipital region of the skull. Of intracranial structures, the brain itself is insensitive. Its pial covering is likewise insensitive except over the great vessels of the circle of Willis, and their chief branches such as the anterior, posterior, and middle cerebral, for a variable distance from their origin. Pain from these structures is referred to the same side of the head, if far from the midline, or bilaterally, if near the midline. From the anterior and middle cerebral arteries the pain is referred to forehead and temple; from basilar to the occiput. The parietal dura mater is sensitive only along the course of the main arteries such as the middle meningeal, from

which pain is referred to the temple on the same side, and along the course of the large venous sinuses such as the superior longitudinal sinus, where the cerebral veins enter. Deflection of the falk, or of the tentorium, also produces pain. Pain from the superior longitudinal sinus and straight sinus is referred to behind or above the eye, from the lateral part of the lateral sinus to the ear. Deflection of the tentorium produces supraorbital pain. The periosteum of the skull is sensitive but the bone not so. Of superficial structures, the galea, muscles, ligaments, arteries, and skin are all sensitive to pain. Pain arising from the more superficial of these deep structures—that is, the coverings of the cranial vault over most of its extent—is referred fairly well to the point stimulated. But with the deeper ligaments, muscles, and tendons of the occipital region, reference over the upper cervical segments is found.

**Fatigue and Psychologic Disturbance.** It is not infrequent for headache to develop in otherwise healthy individuals during times of great mental or emotional stress, or when their tolerance is lowered by infection or other debilitating agents. Such a tendency may be enhanced by a disorder of the mind. In such cases headache tends to occur toward the end of the day, and to be experienced as a dull ache in the forehead which may spread to the temples or occiput; it is not usually throbbing, and usually is relieved by sound sleep. There has been a tendency to assume that this ache arises solely from the mind, but this seems an unlikely explanation. It is accepted that fear and worry may accentuate pain by focusing attention on it, but it is held that the pain itself nearly always has as its basis the stimulation of pain nerves. It is suggested that many such cases result from excessive and maintained contraction of the muscles of facial expression, particularly the frontalis and the muscles of the scalp and neck. It may often be observed in such cases that the forehead is unusually deeply furrowed, and this type of headache can sometimes be abolished by conscious relaxation of the muscles of the forehead and scalp.

A sensation of pressure on the head, particularly on the vertex—as of a tightly fitting hat—is also met with in psychologic disorders, but it is not true headache. It seems that in those with a disorder limited to the mind, the symptoms referred to the head are not so much simple sensations as expressions of the disordered personality.

Aside from the importance of fatigue and psychologic disorders as primary causes of headache, these factors are of great secondary importance in precipitating and aggravating headache due to almost any other primary cause. It is important that the physician should bear this consideration in mind, for if he does not he will be unable to assess the relative parts played in the production of the symptom by local disturbances of the body, and by the mind. And on such assessment must depend his whole therapeutic approach.

### VARIETIES OF HEADACHE

In perusing the following account of headache as we know it today, the reader should realize that the experimental method was used for the first time in the study of headache less than 15 years ago. He will realize that our knowledge is by no means complete, and that both the classification presented and the explanations offered may require modification as knowledge advances. The classification to follow is presented from the standpoint of logical arrangement rather than clinical importance, and hence such frequent causes of headache as migraine and fever are not discussed first. The main classification used here is: (1) headache arising from cranial and extracranial structures, (2) headache arising from intracranial structures, and (3) headache which cannot as yet be classified in this way.

### HEADACHE ARISING FROM CRANIAL AND EXTRACRANIAL STRUCTURES

By their peculiar structure and function the viscera naturally interest the student and practitioner much more than the body wall, and in the case of headache the idea of an intracranial cause occurs most readily. But it is very probable that the cause of headache lies outside the skull at least as frequently as inside.

**Headache Arising from Arteries or Their Neighborhood.** As will be discussed later, there is evidence that dilatation of the temporal arteries, with stretching of surrounding sensitive structures, is responsible for the most of the pain in migraine and some of the pain in febrile headache. In addition, the temporal or occipital arteries may rarely be the seat of a subacute inflammation involving the periarterial tissues and the arterial wall, and often leading to thrombosis of the vessel ("temporal arteritis"). Pain begins in the region of the affected vessel and, as it be-

comes more severe, spreads more widely over that side of the head; sometimes pain is more or less bilateral throughout, though it is not yet certain whether in such cases arteries are affected bilaterally. The pain is dull, with or without a throbbing or shooting element. It is often severe, sometimes interfering with sleep, and commonly lasts for weeks or months. The disease affects old people chiefly, and other manifestations of arterial disease may be found on ophthalmoscopic examination, particularly loss of vision with evidence of obstruction of the central retinal artery or its branches. Other evidence of a constitutional upset may be found, such as fever, malaise, anorexia, or night sweats. The affected arteries of the scalp are always tender and the overlying skin may be reddened; the arterial pulse distal to the lesion is usually lost either temporarily or permanently.

**Headache Associated with Myofibrosis.** In certain cases of headache, tender nodules may be felt near the cranial insertion of the sternomastoids; in muscles near their insertions to the superior and inferior nuchal lines; in the occipitalis, frontalis, and trapezius muscles; or in the temporalis and the galea aponeurotica. Like the tender nodules in myofibrosis of the trunk, the pathologic basis is obscure, and it is also uncertain whether the tenderness of these nodules signifies that pain arises from them or is a secondary consequence of pain. It is thus possible that the tenderness of these nodules and the pain itself are referred from a distant and deep-seated focus, for nodules may be felt in the absence of pain or tenderness, and pain of deep origin is widespread and accompanied by deep tenderness in the area of the pain. The pain, which is of the deep aching type, often begins in a localized area in the forehead, temple, or nape of neck, and spreads to involve one or both sides of the head. It is often precipitated by exposure to cold or draft, and intense paroxysms may be added to an ache which may continue for weeks or months at a lower level of intensity. The pain may be severe but rarely keeps the patient awake at night. It can be abolished in many cases by massage applied to the nodules, but massage may make the pain worse at first. The frequency of this type of headache is disputed; by some it is said to be the commonest of all, but the general opinion seems to be that it is rather uncommon.

#### Headache Arising from Ligaments and Deep

**Structures Attached to the Occiput and Upper Cervical Vertebrae.** If hypertonic saline is injected into ligament, muscle, tendon, fascia, periosteum, or periarticular tissue situated deeply in the neck near the occiput, pain is referred to the back of the head and the nape of the neck on the same side. A similar pain may be seen in spondylitis ankylopoietica and in rheumatoid arthritis affecting the cervical spine. This pain is often produced or increased by movement of the head, and may be found to disappear when ankylosis becomes virtually complete. These structures are also subject to trauma, and occasionally headache initially occipital in distribution is found to follow a sudden flexion, extension, or torsion of the head on the neck. The pain may last days or weeks. Headache arising from these deep cervical structures is not uncommon, but it is often difficult to elucidate the causal lesion.

**The Nasal Accessory Sinuses.** Acute or subacute suppuration in the maxillary antrum gives pain over the antrum or in the forehead. The pain in suppuration of the frontal sinus is frontal, and of the ethmoid and sphenoid sinuses, frontal, vertical, temporal, or occipital. In all cases, pain may be associated with tenderness of the skin in the same distribution. Other signs are usually present, such as nasal or postnasal discharge of pus, fever, and opacity of the sinuses to transillumination or x-ray. The pain may have two remarkable properties; first, when throbbing, it may be abolished by compressing the carotid artery on the same side; second, it tends to recur and get better at the same hours on successive days, most frequently occurring when the patient wakes, and disappearing after the patient gets out of bed. These time relations are generally ascribed to the sinuses filling up during the night, and discharging after the erect posture has been assumed. Although some believe that sinus pain arises chiefly at the nasal orifices of the sinuses, it is generally assumed that the headache arises from the mucous membrane lining the sinus, and that the pain nerves are stimulated by tension. If so, it seems probable that sinus headache, like earache, is usually due to suction on the mucous membrane when aeration is impeded by block; it is then relieved when aeration is affected. X During airplane flight both earache and sinus headache tend to occur on descent when the relative pressure in the blocked viscous falls, rather than on ascent when such pressure rises.

**Eyestrain.** Errors of refraction of the eyes are a well-recognized cause of headache. In such cases pain tends to be referred to the orbit, forehead, and temple, does not throb with the pulse, and tends to occur during intensive use of the eyes as in reading or close work, and to persist for some time afterward. It is particularly obtrusive toward evening, and if the subject is fatigued. There is evidence to show that in the presence of refractive error, use of the eyes produces sustained contraction of the extraocular muscles of the orbit, and of the frontal, temporal, and even occipital muscles, and it is suggested that the pain results from this contraction. A similar mechanism is postulated for the headache of glaucoma. The relief of such refractive errors by use of the correct spectacles abolishes the headache.

### HEADACHE ARISING FROM INTRACRANIAL STRUCTURES

**Histamine Headache.** Although opinions vary concerning the existence and frequency of spontaneous headache due to histamine, the relation of the drug to the symptom is, nevertheless, of some interest, since it was the first kind of headache in which the mechanism of the pain was demonstrated. The headache can be produced easily in a normal subject by quick intravenous injection of 0.1 mg. of histamine acid phosphate. Headache begins about a minute after the injection, as the facial flush is beginning to fade, is maximal at about the second minute when the flush is nearly gone, and disappears about the eighth minute (fig. 1). At first, it throbs conspicuously with each beat of the pulse, but is felt in both sides of the forehead, and at its height extends to the vertex and occiput. It can be established that:

1. Headache does not arise from an extracranial structure, because arrest of the circulation to the scalp before injection of histamine does not prevent the pain.
2. Headache arises from a structure innervated by the trigeminal nerve, since it does not occur on that side of the head when the sensory root has been severed or the ganglion injected with alcohol.
3. It probably arises from the meninges, as it is greatly increased by shaking the head gently, and the meninges are the structures which will be chiefly strained in this movement.
4. It arises from the territory supplied by the

internal carotid artery, since injection of histamine into the internal carotid produces headache, but injection into the external carotid does not.

The most striking events following the intravenous injection of histamine are consequences of

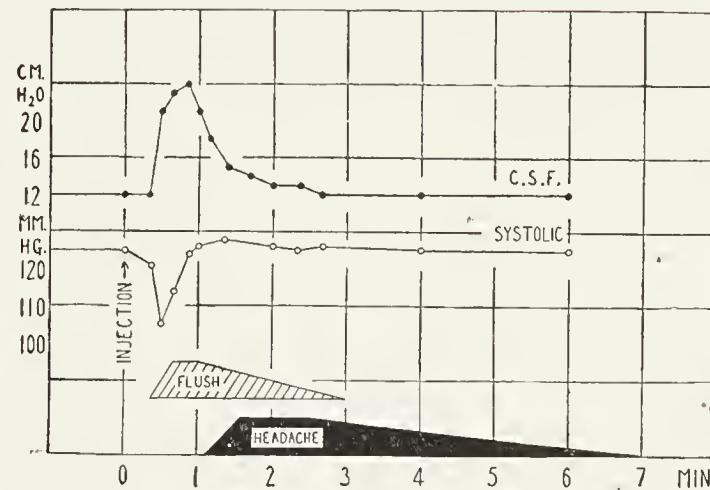


Fig. 1. Chart showing the course of the cerebrospinal fluid pressure (C.S.F.), the systolic blood pressure, the facial flush, and the headache following intravenous injection of 0.1 mg. of histamine. (Courtesy, Pickering: *Clin. Sc.*, 1:82, 1933.)

vasodilatation; thus the face flushes, the blood pressure falls, and the cerebrospinal fluid pressure rises. Curiously enough, headache begins only when these signs of vasodilatation are subsiding, and, in fact, is prevented from appearing by the phenomena occurring during the phase of obvious vasodilatation. Thus, when histamine is slowly infused into a vein, headache does not usually appear until after the infusion is stopped; and an established headache is temporarily relieved at the moment the face flushes after a second injection of histamine. It can further be shown that any event which leads to a fall in arterial pressure tends to relieve the histamine headache, as does any event which tends to increase the cerebrospinal fluid pressure. Thus the headache throbs with the pulse and is abolished on the same side of the head by digital obliteration of the common carotid artery. The headache is relieved by compression of the jugular veins, or by injecting saline into the subarachnoid space, both of which raise cerebrospinal fluid pressure. These facts are most easily explained by supposing that headache results from stretching of pain-sensitive tissue around the large intracranial arteries derived from the internal carotid, such as the anterior and middle cerebral. It is supposed that these arteries are relaxed by histamine but that the headache does not occur when they are

prevented from expanding by low blood pressure and high intracranial pressure.

It is probable that a similar mechanism is concerned in producing the headache of fever.

**Lumbar Puncture Headache.** A very characteristic headache occasionally occurs a few hours to a few days following lumbar puncture, and particularly if the patient has been allowed up, or if several attempts have been made to enter the spinal theca. The headache is usually, but not always, throbbing, and is felt chiefly in the occiput but also widely over the cranial vault, and the pain may spread into the neck and back. It may be accompanied by vomiting and neck rigidity, and other signs of meningeal irritation. The most characteristic feature of the headache is its very conspicuous increase when the patient sits up, and its relief on lying down. The headache is caused by leakage of cerebrospinal fluid along the tract left at lumbar puncture. For if, when the headache is present, a second lumbar puncture is performed with the patient horizontal, the pressure of cerebrospinal fluid is found to be zero, and if the pressure is restored by the injection of normal saline into the theca, the headache is abolished, though it usually returns after some hours, presumably because the leakage continues. The headache is increased by compression of the jugular veins, and is usually unaffected by digital obliteration of one carotid artery. From these facts it seems probable that the headache results from the tension exerted on some pain-sensitive structure by the caudad displacement of the brain, consequent on the emptying of cerebrospinal fluid from the subarachnoid space, and impairment of the cushioning effect of the fluid. Tension on the venous attachments of the brain to the great dural venous sinuses seems the most likely mechanism.

The occasional occurrence of headaches following lumbar puncture has led some to adopt the point of view that all patients should be kept in the recumbent position following the procedure. Headache following cisternal puncture is rare.

**Raised Intracranial Pressure.** Headache is an outstanding symptom in a number of diseases in which intracranial pressure becomes elevated, and the suggestion has been widely accepted that such headache results from stretching the pain-sensitive parietal dura mater. This hypothesis must now be rejected for the following reasons:

1. It is difficult to see how the parietal dura mater, supported as it is by the bony skull, can be stretched by a rise in intracranial pressure, except at the various foramina of the skull.

2. The cerebrospinal fluid pressure may be raised to very high levels (500 or 600 mm. H<sub>2</sub>O) by injecting saline solution into the subarachnoid space at lumbar puncture or by jugular compression, without headache resulting.

3. A critical examination of the behavior of headache in several diseases reveals facts which cannot be reconciled with the hypothesis. These facts will be described separately, under the several diseases.

**Meningitis.** One of the most severe headaches is that associated with meningitis—particularly the acute inflammations produced by the pyogenic microbes, the meningococcus, streptococcus, pneumococcus, and staphylococcus; in the less acute tuberculous meningitis, headache is often less intense. The headache is more or less generalized over the calvarium, and may be throbbing or not; it is associated with rigidity of the neck muscles, so that when the head is flexed the neck muscles contract strongly and pain is felt in the occiput and neck; Kernig's and Brudzinski's signs may also be present but are less reliable. The patient commonly lies on his side with the head extended and the hips and knees flexed, and he shuns the light. This headache is very greatly increased by shaking the head, and the patient may resent any movement of his bed.

In all forms of meningitis the cerebrospinal fluid pressure is commonly raised, sometimes to very high levels of over 600 mm. H<sub>2</sub>O, and it is not infrequent to find that removal of cerebrospinal fluid by lumbar puncture relieves the pain (fig. 2). Nevertheless, it is found that if the pressure is reduced still further—below the normal level—pain is increased, to be relieved by reinjection of fluid and restoration of pressure to normal. It seems probable that in this instance pain is due to a chemical irritation of the pain nerve endings of the meninges, consequent on the tissue damage of bacterial action; and that mechanical distortion of these inflamed tissues, as by distention or depletion of the subarachnoid space, may further increase pain. The mechanism of pain thus is probably identical with that occurring in acute inflammatory conditions elsewhere, such as those affecting the pulp of the finger and the peritoneum.

**Cerebral Tumor.** Headache in cerebral tumor at first occurs in attacks lasting only a few seconds to three hours, and typically about one hour. The paroxysms may be precipitated by any activity, especially such as involves abrupt changes in

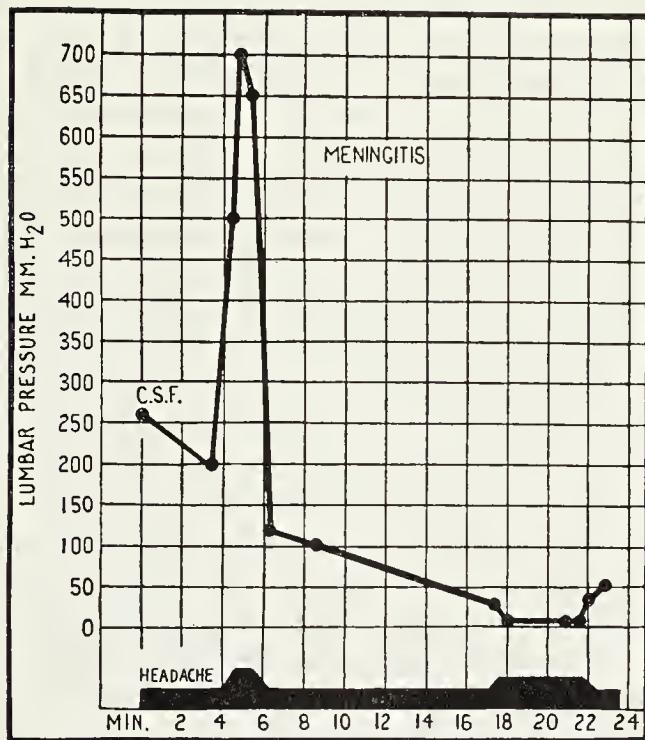


FIG. 2. Chart showing the relationship of headache to C.S.F. pressure in a case of meningococcal meningitis in which the pressure was altered by withdrawal of C.S.F. and injection of saline through the lumbar puncture needle. (Courtesy, Pickering: *Brit. M. J.*, 1:907, 1939, fig. 2.)

position of the head, and they diminish in frequency when the patient is kept in bed. With the patient at rest the attacks are often frequent at night, waking the patient, or they occur when the patient wakes in the morning. Usually no simple event is found to abolish the pain, and relief is sought from anodynes and bed rest. Frequently, as the tumor grows, headache may increase in frequency, duration, and intensity. In the later stages the pain may become continuous. The pain may be slight, but can be intolerably severe. In fact, the most severe headaches occurring in disease are those of meningitis and tumor, rivaled only by that of intrathecal air insufflation. Brief paroxysms of most intense headache, during which the subject writhes in agony and is oblivious to events around him, are highly suggestive of tumor. Headache is essentially a deep, aching pain, though the epithets used vary with the patient's experience, imagination, and command

of language. The pain may throb with the pulse or it may be continuous or "smooth." Not infrequently the headache is accompanied by nausea or vomiting. In some cases the two are related, vomiting occurring with the worst but not with the least pain; but vomiting also occurs in tumor without headache, and it occurs without preceding nausea.

Most frequently in tumor, headache is bilateral and frontal, but there is some relation between sites of pain and tumor. Thus occipital headache is more frequent with tumors below than with those above the tentorium, and when headache is unilateral the tumor is on the same side in about 70 per cent of cases. Sometimes headache is localized to an area roughly 5 cm. in diameter, which may correspond fairly closely to the site of the tumor. Headache is more frequent in quickly growing tumors, such as gliomas, than in the slower growing varieties, such as meningiomas. It is also more frequent and begins earlier when the mass is smaller in tumors involving the ventricles, or below the tentorium, than when the frontal or parietal lobes are involved; tumors of the temporal and occipital lobes occupy an intermediate position.

It may be accepted that the afferent impulses responsible for tumor headache arise within the cranial cavity, for, as will be mentioned, pain can be induced and relieved by procedures which affect only the cranial content; also that the stimulus is mechanical, for the common effect of such procedure is to alter the stresses and strains inside the skull. The stimulus is probably not stretching of the parietal dura mater by raised intracranial pressure, because:

1. In a given case, cerebrospinal fluid pressure measured in the presence of headache is not significantly higher than in its absence.
2. Lumbar puncture may relieve, but it may also increase or induce, headache.
3. Raising intracranial pressure by jugular compression, or by intrathecal injection of saline, may relieve as well as increase headache in cerebral tumor.
4. It has been shown at operation under local anesthesia that headache may sometimes be reproduced by emptying or distending the ventricles on the same or opposite side.

From these experimental findings, as well as from the clinical features of headache, it seems that sudden changes of intracranial pressure,

either up or down, may precipitate pain. Two ideas of the origin are widely entertained: that it arises from the arteries at the base of the brain, and that it arises from tension on the dural attachments of, and supports for, the brain. The first explanation finds support in the observation that histamine may, in a given patient, reproduce precisely the headache of tumor, even when this has a highly individual localization. The second explanation is not easily compatible with certain details of observations made on individual cases, though it agrees with much of the evidence; for it is well known that tumor gives rise to distortions of the intracranial septums and that such distortions can give rise to pain, presumably, by tension on the pain-sensitive tissues around the dural sinuses. That headache is due to such distortion would be in harmony with many of the facts about tumor headache; namely, that it may be either relieved or increased by lowering cerebrospinal fluid pressure, that the headache may frequently be relieved by intravenous or rectal injections of hypertonic solutions, and that the headache may disappear following operations for decompression. Moreover, this hypothesis would be compatible with the early paroxysmal and later continuous duration of headache, and with its high incidence in posterior fossa and rapidly growing tumors.

**Cerebral Hemorrhage.** Headache is a constant feature of spontaneous subarachnoid hemorrhage resulting from rupture of a miliary aneurysm of the circle of Willis or its main branches, and the stories given by such patients indicate that headache must begin at about the time when the aneurysm ruptures. Thus, a patient who up to that time has been perfectly well is seized abruptly with the most severe generalized headache, and a few moments later sinks to the ground unconscious. The headache is invariably severe when the patient recovers consciousness, and lasts for some days or weeks afterward. It has been supposed that the headache arises, as does that of meningitis, from inflammation of the meninges evoked by the presence of blood, and it is true that neck rigidity is a constant feature of subarachnoid hemorrhage, as it is in meningitis. Nevertheless, the idea that blood can or does provoke pain from a sensitive serous membrane is not supported by a critical examination of the facts concerning the peritoneum or pleura, in both of which the presence of blood may be pain-

less. The alternative view is that the pain arises from the pain-sensitive tissue in the region of the aneurysmal sacs; and it is possible that sudden stretching of the perivascular tissue, with consequent headache, may precede the actual rupture into the subarachnoid space. However, it is to be noted that accounts of pain produced at operation by stimulating the great vessels at the base of the brain describe pain as unilateral, while in subarachnoid hemorrhage it is nearly always bilateral. Moreover, there is evidence from intracranial aneurysm that headache from the region of the artery is more localized, for in unruptured aneurysms headache occurring in paroxysms restricted to the same side of the head is common.

Headache may also occur in cerebral hemorrhage from intracerebral rupture of an artery as a consequence either of hypertension or of atheroma, but it is a rare complaint, as such patients usually die. When survival occurs, headache is frequent. Cerebral thrombosis and cerebral embolism are not associated with headache. The idea that the imminence of cerebral hemorrhage can be foretold by headache is, in general, entirely without foundation, but has obvious commercial value and appeals to the intellectually feeble or the morally unscrupulous.

#### OTHER FORMS OF HEADACHE

**Migraine.** Classic migraine presents a dramatic sequence of events. On waking in the morning the patient may feel slightly confused and unable to see quite clearly. Within a few minutes bright spots appear in one half of his field of vision, arrange themselves as a zigzag pattern which subsequently fragments and fades, to be followed by blackness of that visual field. As sight gradually returns, headache begins as a dull, boring, throbbing pain in the opposite temple, gradually increasing in intensity until the whole of the same side of the head is affected. The patient is now pale and prostrate and can get relief only by lying down in a quiet and darkened room, where, after some time, he falls into a deep sleep from which he awakens well. In most attacks nausea and vomiting occur either throughout or at the height of the headache, which may, in fact, be relieved by vomiting. Much variation occurs. Thus any of the three components—aura, headache, or vomiting—may be absent. The aura may be quite different from the classic form described; though usually visual, it may

involve other forms of sensation. And although headache is classically unilateral, it may be bilateral. Diagnosis in classic cases is easy but in some may be difficult or impossible. A familial incidence is common.

Over a century and a half ago Parry observed that the headache of migraine could be relieved temporarily by compressing the common carotid artery in the neck on the same side. In 1867 Mollendorf wrote,

If the common carotid artery be compressed on the painful side at the level of the thyroid cartilage during the hemicranial paroxysm so that the pulse in the temporal artery begins to fail, the headache vanishes as if by magic . . . With the intermission of the compression, with the first full pulse wave the pain begins afresh and, indeed, the first pulsation will be felt to be much more painful . . . Conversely, compression of the other side enhances the pain.

In certain cases complete relief of pain is obtained by digital obliteration of the temporal or occipital arteries or both; in others it is not, and complete relief can be attained only by compression of the common carotid. It seems, therefore, that in many cases of migraine, headache arises entirely from stretching of the walls of the large arteries of the scalp—temporal, occipital, or frontal—and it can be shown (1) that a similar pain can be evoked by stretching the walls of these arteries exposed surgically and (2) that ligature of the arteries may abolish the attacks of headache. In other cases, however, it must be presumed that at least some of the pain must originate similarly from dilatation of the middle meningeal artery. The headache of migraine often may be relieved quickly by intravenous injection of ergotamine tartrate, or aborted if the injection is made before headache starts, and it has been shown that the drug constricts the scalp arteries. Although some believe that cerebral vasoconstriction is responsible for the aura, the available evidence favors the view that the headache of migraine is due to expansion of walls of arteries, chiefly extracranial. However, so far, no other superficial arteries have been shown to give rise to pain when they expand. How this expansion is brought about in migraine, why it should not be produced by physiologic measures such as heat, and what its relationship is to the presumably intracranial events responsible for the aura, are unknown. That emotional disturbances are of great impor-

tance as precipitating factors cannot be doubted; that they are the underlying cause remains to be demonstrated. Many believe allergy to be the dominant factor; for this there is little evidence.

It should not be forgotten that what appears to be migraine may be due to an organic cause—for example, cerebral tumor or hypertension. Attacks of seemingly true migraine may be followed by ophthalmoplegia; this syndrome of ophthalmoplegic migraine is most often due to a congenital aneurysm of the internal carotid or anterior cerebral artery.

**Hypertension.** Headache is probably the commonest symptom of hypertension. It may be troublesome and may be severe; and in this respect it is more comparable to migraine and tumor than to meningitis. Characteristically, the pain is occipital, and is noticed on waking in the morning, to improve as the day advances; it may last an hour or longer. The headache may be associated with nausea and vomiting. Over a large series of cases there is some relationship between intensity of headache and intensity of hypertension, and the severest headaches are thus commonly found in hypertension of the malignant type. As papilledema also occurs in malignant hypertension, and cerebral thrombosis is by no means rare, a mistaken diagnosis of cerebral tumor may be made unless the level of the blood pressure and the total clinical picture are taken into consideration.

The precise mechanism of headache in hypertension remains obscure. The cerebrospinal fluid pressure is raised in rough proportion to the diastolic arterial pressure, but is the same in the presence and absence of headache. That the headache may have an intracranial source is indicated by its often being increased by withdrawal of cerebrospinal fluid at lumbar puncture. Evidence has been produced to show that headache of hypertension is often due to stretching of the walls of extracranial arteries. Thus the headache is said to be relieved by compression of the superficial arteries supplying the scalp, and abolished by tying these arteries. Pain is often uninfluenced by carotid artery compression; nor is its morning incidence dependent on whether the patient sleeps with one or several pillows.

**Fever.** Headache occurs in many diseases in which the temperature rises—for example, acute tonsillitis, typhoid fever, malaria, and sandfly

fever. The pain may be throbbing with the pulse or steady, and may be frontal, occipital, or generalized. The headache is very like the histamine headache in being relieved on the same side by carotid artery compression, on both sides by compression of the jugular veins, or by the injection of saline into the subarachnoid space; it is increased by shaking the head. Like histamine headache, pain is temporarily relieved by injection of histamine or amyl nitrite during the time the arterial pressure is lowered and the cerebrospinal pressure raised by these drugs. It seems probable, therefore, that the headache arises in the same way as that following histamine—namely, from stretching of pain-sensitive tissue around the large arteries at the base of the brain. In certain cases, however, pain may be lessened by compression of temporal or angular arteries, and in these a component of the headache seems to be derived from the walls of extracranial arteries, as in migraine.

**Anemia.** Some patients suffering from severe anemia experience headache which is abolished when the hemoglobin content of the blood is restored by treatment. The headache is usually frontal or generalized, and may or may not be throbbing. It tends to occur toward evening. This headache has been insufficiently investigated to reveal its mechanism. Headache is, however, a common experience after exposure to high altitudes and thus to oxygen lack, and it is tempting to suppose that the two may be related. Curiously enough, if exposure to a high altitude (over 14,000 feet) is brief—say four hours—headache is experienced not during the exposure, but afterward. The explanation of this curious fact is unknown. Likewise, the explanation for the headache which may occur in patients with polycythemia is uncertain.

**Post-traumatic.** After head injury, especially one that has caused loss of consciousness, over 50 per cent of patients suffer from headache. Other associated symptoms are dizziness, amounting to a sense of instability rather than to true vertigo, and mental change, of which loss of memory and inability to concentrate are the chief signs.

Considerable divergence of opinion exists as to the mechanism of headache in such cases. In a small series with dull pain more or less localized to the area of injury and persisting up to eight years afterward, Penfield recorded localized

changes in the subarachnoid and subdural spaces. This was revealed by air insufflation into the spinal theca, and the usual relief of headache after such insufflation. In cases not so relieved, he reported success from dividing adhesions formed near the site of injury between the dura and piaarachnoid. Consequently, he ascribed the headache in these cases to tension set up in these adhesions between the brain and its coverings, the adhesions being formed when the brain was out of place due to the local tissue reaction to injury. The fuller experience of the late war suggests that headache of this type and origin is uncommon. More usually, the headache is bilateral, frontal, or generalized, often throbbing, and usually occurring in paroxysms or liable to paroxysmal exacerbations. The paroxysms may be induced by stooping, physical exertion, noise, and excitement. The pain may be increased by lying down and relieved by raising the head on pillows, or relieved by recumbency, and is worst in the erect posture. These observations suggest an organic cause for the headache, but the nature of this has not been worked out. The headaches usually pass off with the improvement of the patient, consequent on modern rehabilitation management, and they are relieved by the ordinary anodynes.

The evolution of post-traumatic headache is often complicated by the presence of economic problems in relation to compensation.

#### APPROACH TO THE PATIENT WITH HEADACHE

From the foregoing account it will be appreciated that certain forms of headache may be diagnosed and others suspected, when a lucid description of the pain has been obtained from the patient. Headache occurring toward the end of the day and relieved by sound sleep may be due to fatigue or eyestrain; that due to a disturbed mind is less often relieved by sleep. Paroxysmal headache, often unilateral, preceded by an aura and accompanied by vomiting is recognizable as migraine. Occipital headache occurring on waking, and declining as the day wears on, usually is due to hypertension. Headache persisting without remission for weeks or months, and unaccompanied by other manifestations of disease, is commonly due to an affection of the deep structures of the neck and head, such as myofibrosis; occasionally, its abrupt onset following

sudden movement indicates a traumatic lesion. Following head injury, headache is common and often associated with dizziness, inability to concentrate, and impaired memory. Headache recurring over short periods, at a definite hour of the day, suggests a sinus infection. Headache that is accompanied by symptoms of fever and acute infection probably is due to a febrile illness; when meningitis is present the headache is very severe and neck rigidity is almost invariable. Headache occurring in brief and severe paroxysms, becoming recently longer and more frequent, is suggestive of cerebral tumor; the headache has localizing value. Sudden severe headache, followed by loss of consciousness, suggests a cerebral hemorrhage. After lumbar puncture, headache may develop when the patient sits up and may be relieved when the patient lies down.

These points in the history which have been noted are very important; but they are often no more than pointers as to what investigations should be carried out in a specific case. Many of the conditions named have physical signs that should be sought. It is equally important that the physician should try to assess the contribution made by disturbances of the mind. While mental disturbance per se produces a feeling of

pressure or confinement of the head rather than ache or pain, pain may arise from secondary effects on the muscles of the head and neck, and any pains, however trivial, may appear severe to a mind that is tormented with fear or doubt.

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## 3

### Pain in the Chest

William H. Resnik and T. R. Harrison

#### Pain Arising from the Heart

Pain Due to Myocardial Anoxia

Pericarditis

Cardiac Neurosis

#### Pain Arising from Intrathoracic Viscera Other than the Heart

Pain Arising from the Aorta

Pain Arising from the Pulmonary Artery

Pain Arising from the Lungs, Bronchi, Pleura, and Mediastinum

Pain Arising from the Esophagus

Pain Referred to the Chest from Abdominal Organs

Pain Arising in the Chest Wall

Differential Diagnosis

There are four general regions from which chest pain may arise: (1) Heart; (2) intrathoracic

organs other than the heart; (3) abdominal organs; and (4) chest wall. Of these, the recognition and differentiation of the pains originating in the heart are most important from the standpoint of frequency, potential gravity of some of the responsible disorders, and the apprehension, on the part of the patient, as to their cause and significance. Considering the seriousness of the issues involved, in the analysis and evaluation of hardly any other symptom is the history an instrument of such vital importance; for in some instances, on the character of the symptoms

alone, and without help from either the physical examination or special procedures, may depend a crucial diagnosis.

In the great majority of instances a person complaining of pain in the chest will be found to be suffering from one of the following disorders, the more common and important of which are *italicized*:

I. Pain arising from the heart:

A. Pain due to myocardial anoxia:

1. *Angina pectoris*
2. *Myocardial infarction*
3. *Coronary insufficiency*

B. *Pericarditis*

C. *Cardiac neurosis*

II. Pain arising from intrathoracic viscera other than the heart:

A. The aorta:

1. Complications of syphilitic aortitis
2. Dissecting aneurysm

B. The pulmonary artery:

1. *Pulmonary embolism*
2. Pulmonary hypertension

C. The lungs, bronchi, pleura, and mediastinum:

1. *Pleuritis*
2. Pneumothorax

D. The mediastinum:

1. Mediastinal emphysema
2. Enlarged lymph nodes

E. The esophagus:

1. *Heartburn*

III. Pain referred to the chest from abdominal organs:

A. The stomach:

1. Distention resulting from *aerophagia* and *pylorospasm*
2. Abnormal pouches (*hiatus hernia*, etc.)

B. Biliary tract disease, with atypical radiation

C. Spleen (especially infarction)

D. Pancreas (inflammation and neoplasm)

E. Splenic flexure (gaseous distention)

IV. Pain arising in the chest wall:

A. The vertebral column (*spondylitis*, neoplasm)

B. Displaced costal cartilage

C. Scalenus anticus syndrome

D. Pectoral muscles ("charley horse")

E. Skin (*herpes zoster*)

F. "*Coronary shoulder pain*" (i.e., reflex sympathetic dystrophy)

This list does not include all of the possible causes of chest pain but is reasonably comprehensive, and anyone who has a clear comprehension of the clinical features of these several conditions will make few mistakes in the evaluation of this symptom.

The afferent sensory fibers from the heart pass via the sympathetic pathway to the upper four dorsal posterior roots, and thence into the spinothalamic tracts. It should be noted that other thoracic structures, including the aorta, esophagus, mediastinum, pleura, etc., as well as portions of the chest wall, possess sensory nerves with the same general afferent course. Hence the location of chest pain has limited value as a clue to the organ involved.

In certain patients pain arising in the heart may be referred to the neck, jaw, ear, or abdomen. The reasons for such bizarre behavior of cardiac pain remain obscure.

## PAIN ARISING FROM THE HEART

### PAIN DUE TO MYOCARDIAL ANOXIA

#### HISTORICAL REVIEW

In 1768, in a brief communication, William Heberden described for the first time the condition that he named *angina pectoris*. The relationship between disease of the coronary arteries and *angina pectoris* was soon recognized by Jenner, Fothergill, and Parry, and the latter wrote in 1799: "Though a quantity of blood may circulate through these arteries, sufficient to nourish the heart, as appears, in some instances, from the size and firmness of the organ, yet there would probably be less than what is requisite for ready and vigorous action. Hence, though a heart so diseased may be fit for the purposes of common circulation, during a state of bodily and mental tranquillity, and of health otherwise good, yet when any unusual exertion is required, its powers may fail under the new and extraordinary demand." With the passage of time, and for a variety of reasons, the concept grew that *angina pectoris* was a neurosis, and to the original and clear picture of Heberden's

were added a number of syndromes, all entitled angina pectoris; finally, they had in common only the symptom of pain or other discomfort in the region of the heart. In recent times two dominant theories emerged, one ascribing angina to cardiac ischemia, and the other to distention of the diseased root of the aorta. The crystallization of the modern view began with the clinical reports by Obrastzow and Straschesko, and by J. B. Herrick, on acute coronary thrombosis and myocardial infarction, and with the experimental work by Fred Smith on the electrocardiographic findings following acute coronary occlusion. Further strengthening came through the demonstration by Feil and Siegel that characteristic changes could be detected in the electrocardiogram during the attack of angina, and the subsequent exposition by Keefer and Resnik of the theory that all cases of angina pectoris could be explained on the basis of relative myocardial anoxia, even when disease of the coronary arteries was not present.

#### ANGINA PECTORIS

Angina pectoris is a syndrome characterized by pain, continuous and not intermittent, usually felt as a constriction or sense of pressure (less commonly aching or burning) behind the sternum, less frequently in the precordium or elsewhere, and sometimes radiating to the upper extremities, neck, or jaws. The pain is provoked by walking, emotional strain, or any other stimulus that increases the work of the heart, and it is relieved promptly as the additional burden on the heart is removed. The natural history of angina pectoris is characterized not only by the type of pain which has been described but also by the likelihood of sudden death. Even though this complication may never materialize, there is no way of predicting the instances in which it will occur, and hence the threat of sudden death is present in all cases.

It is now generally accepted that the basis of angina pectoris is a physiologic disturbance: a disproportion between the oxygen supply and the oxygen needs of the myocardium. A brief discussion of the important factors governing these functions (i.e., oxygen supply and oxygen need) follows:

The oxygen supply to the heart is determined mainly by: (1) *The caliber of the coronary arteries*, which may be affected by structural alterations

(narrowing by coronary sclerosis, or closure of a coronary ostium by syphilitic changes in the aorta, by thrombosis, or by embolism); or by physiologic changes (dilatation by chemical metabolites and reflexes causing either dilatation or constriction); (2) *the blood pressure*, the flow being generally proportional to the mean pressure, the greater fraction of the flow taking place during diastole; (3) *the heart rate*, an increased rate in conjunction with an augmented pulse pressure (larger cardiac output) being associated with an increased coronary flow; an increased rate accompanied by a diminished pulse pressure resulting in a decreased coronary flow; (4) *the hemoglobin content* per unit of blood.

The *oxygen needs* of the heart are governed primarily by the amount of work that it performs. (1) The increased demand may be *temporary*, as during exercise, emotional strain, after eating, or when the heart rate is elevated, as in paroxysmal tachycardia. (2) The increased demand may be *permanent*, as in aortic stenosis or hypertension.

In general, the combined effect of these various factors determines the balance between the oxygen needs and supply of the heart. With them in mind, it becomes possible to explain the circumstances under which the pain of angina pectoris appears. In the vast majority of cases an organic narrowing of the coronary arteries exists, usually the result of arteriosclerotic changes. In these cases the supply of blood (oxygen) is sufficient to meet the requirements of the heart at rest or during mild exercise. When the work of the heart is increased, as by *exercise* or after *eating*, or by *emotional strain*, the obstruction in the artery prevents the increased flow that automatically ensues in the normal individual by virtue of the enhanced mean and pulse pressures, and by coronary dilatation (reflex and chemical). Anginal distress may also appear in *paroxysmal tachycardia*, due mainly to the combined effects of increased rate of the heart and diminished coronary flow. Likewise, anginal pain may occur during an attack of *hypoglycemia* (chiefly the result of increased work of the heart, possibly also because of the disturbed sugar metabolism in the myocardium); or in severe *anemias* (diminished oxygen-carrying capacity of blood); or in *thyrotoxicosis* (increased work and also increased basal oxygen requirements of the heart); or in

conditions definitely or possibly associated with increased release of epinephrine (adrenal medullary tumor, anesthesia, emotional disturbances, etc.).

Reflex coronary constriction may also play an important role in some instances, being the mechanism responsible for the facts that anginal pain is more easily provoked on exposure to cold, or induced by *digestive disturbances*. Moreover, it is the only satisfactory explanation for the occurrence of angina pectoris under circumstances when, so far as can be ascertained, none of the other known responsible factors are operative.

A factor which has received relatively little attention, and which may possibly be of importance in certain cases, is delay in reflex coronary dilatation when exercise is undertaken. Such a mechanism, which is probably of no importance except in the presence of coronary disease, may account for those instances in which the pain appears on effort and then disappears, even though the exercise be continued at the same rate.

Ever since the latter part of the eighteenth century, when cardiac ischemia was suggested as the cause of angina pectoris, the almost constant association of coronary disease with this condition has been widely recognized. Nevertheless, the occasional occurrence of angina without coronary disease proved to be one of the most important stumbling blocks in the way of complete acceptance of the cardiac ischemia theory, until it was appreciated that practically all these exceptional cases were associated with lesions of the aortic valve. In cases of aortic regurgitation due to syphilitic aortitis, the valvular lesion frequently is accompanied by narrowing or complete closure of one of the coronary ostiums, and diminished coronary flow on this basis alone is sufficient to account for the anginal pain. When the aortic regurgitation is unassociated with disease of the coronary arteries, as is true in some syphilites and in practically all cases of rheumatic aortic insufficiency, angina pectoris may still occur as a result of the impaired coronary flow stemming from the low diastolic and, hence, the low mean blood pressures found in these conditions. In recent years it has been found that *aortic stenosis* (with but little or no detectable regurgitation) is an even more common cause

than aortic insufficiency for the development of angina pectoris, and here it may be attributed to the greatly increased expenditure of energy (and, hence, oxygen need) occasioned by the obstruction to the outflow of blood from the ventricular cavity through the narrowed aortic orifice.

Occasionally, anginal pain may occur in *anemia* (reduced oxygen capacity of blood), and may then disappear as the disturbance in the blood is overcome; or angina may develop following the onset of shock caused by hemorrhage, pulmonary embolism, or injury (diminished coronary flow due to lowered mean blood pressure).

The enumeration of these varied factors responsible for the appearance of angina pectoris tends to make the subject appear more complex than it really is. Actually, *in the vast majority of cases, the underlying cause of the development of angina pectoris is disease of the coronary arteries, producing a more or less serious impediment to the flow of blood through these vessels*. While the literature contains reports of rare cases of angina pectoris in presumably normal hearts caused by paroxysmal tachycardia, anemia, or hypoglycemia, in the great majority of cases where these conditions as well as thyrotoxicosis and shock have been associated with angina, they have acted as aggravating or precipitating factors, and have superimposed their effects on a heart whose coronary flow has already been compromised by coronary disease. For practical purposes it is safe to assume that only in the occasional case of aortic valvular disease may one encounter angina pectoris in the absence of a seriously impaired coronary artery system.

For a number of years it has been known that collateral channels may exist between the coronary arteries or between the cavities of the heart and the coronary arteries. In a certain percentage of cases, probably small extra-coronary communications play an important role in nourishing the heart when the flow through the coronary arteries is inadequate. Recent observations have indicated, more emphatically than has hitherto been appreciated, how extensive may be the damage in the coronary arteries and the growth of the intercoronary artery anastomoses. Whether or not cardiac pain or necrosis ensues depends primarily on the

efficiency of these collaterals, and on whether their growth can keep pace with the occluding lesions. In a high percentage of cases of angina pectoris, at least one—usually more—complete occlusion of the coronary arteries can be demonstrated. These investigations also point out the fallacy of accepting even an autopsy report exonerating the coronary arteries, particularly when anginal symptoms have been present during life, unless extremely precise technic has been employed.

The exact nature of the pain-producing substance is as yet unknown. It has been assumed that the pain has been caused by the accumulation of metabolites not yet identified.

**Procedure in Suspected Cases of Angina Pectoris.** Usually the history is of greatest importance in establishing the diagnosis of angina pectoris. When a characteristic substernal discomfort, however mild, is brought on by exertion and relieved promptly by rest, the diagnosis of angina pectoris can be made with reasonable assurance, even though the examinations, including the x-ray and the electrocardiogram, prove to be entirely negative. If, however, doubt exists because of the atypical character or location of the pain, or if the relationship to exertion and rest is not clear, or if the story is uncertain because of the age or sex of the patient, further observations may be necessary: (1) Most important is the determination of the influence of exertion and rest on the pain, and

this usually can be accomplished most conveniently by having the patient climb one or more flights of stairs, or undertake a standing-running exercise, under the observation of a physician. (The exercise test is simple and appears to the writers to be preferable to more complicated procedures such as the induction of arterial anoxia.) Pain may be provoked more readily if the exercise is taken shortly after eating, or with the patient holding a cube of ice in one hand. (2) The influence of nitroglycerin ( $\frac{1}{150}$  or  $\frac{1}{200}$  gr. under the tongue) should be noted, given either just prior to the exercise to determine whether the tolerance for exercise is increased, or immediately after the appearance of the pain to observe the rapidity with which the discomfort is relieved. In either case the nitroglycerin should exert an unmistakably beneficial effect in cases of anginal pain. (3) Electrocardiograms taken during an attack of pain, spontaneous or induced, may show characteristic alterations in the RST segments or in the T waves (fig. 3; see also Chapter 31, figure 75). (Positive results are obtained by this procedure in 25 to 60 per cent of cases of angina pectoris, depending on the criteria employed.) Control records should be taken before and after the paroxysm of pain. Between attacks of pain, the electrocardiogram may be normal or may reveal abnormalities indicative of myocardial damage, but none of these tracings can be considered diagnostic of angina pectoris.

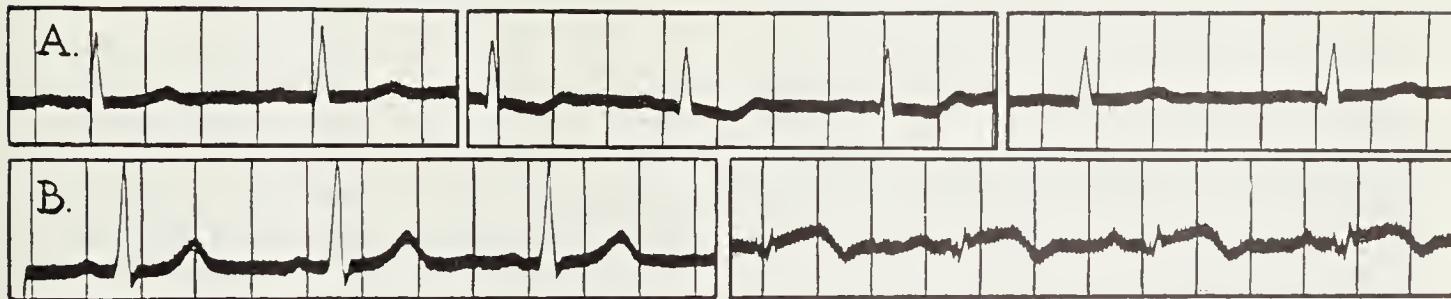


FIG. 3. Angina pectoris (A) vs. myocardial infarction (B). (H. H. Hecht.)

The electrocardiogram in patients suffering from angina pectoris is more often normal than abnormal. When the subject is placed under stress (exercise, low oxygen inhalation), electrocardiographic changes are likely to appear. They usually consist of depression of the RST segment and inversion of T waves (A). They are strikingly different from the QRS, ST, and T wave changes characteristic of acute myocardial infarction (B).

When a patient with a previously normal electrocardiogram is seen during an episode of precordial distress, the record may show unspecific T wave changes. This may be taken to indicate angina pectoris or, less commonly, may be the result of unspecific electrocardiographic changes secondary to intrapulmonary, mediastinal, or vascular episodes associated with chest pain. If, however, the electrocardiogram shows diminished R waves with prominent Q waves, and elevation of the RT segment with or without inversion of the final portion of the T wave, an acute myocardial infarction is almost invariably present (see also Chapter 31, p. 79).

(A) A 52-year-old veteran; angina of effort. Lead II before, during, and after inhalation of 10 per cent oxygen in nitrogen.

(B) A 44-year-old salesman; acute myocardial infarction. Lead V4 before and immediately after an episode of chest pain.

### *Anginal Attacks at Rest*

Patients with angina, who live long enough, nearly always develop typical attacks at rest. These may occur at any time but seem especially prone to appear in the recumbent posture. Occasionally, the malady may be ushered in by attacks of angina that appear only at rest. Ultimately, the distinguishing hallmark, angina on exertion, will usually develop, and whatever doubts concerning the nature of the attacks that may have been entertained will then disappear. However, in the stage where only attacks unrelated to exertion occur, the diagnosis may be exceedingly difficult, for other conditions, such as hiatus hernia, may simulate every feature of the pain of angina pectoris, aside from the characteristic relationship to exertion. Careful study of these cases of angina of rest may uncover precipitating factors such as emotional strain (and vivid dreams), paroxysms of tachycardia, bouts of hypoglycemia, or an adrenal medullary tumor. In other cases, reflex coronary constriction may afford the probable explanation (cold bedclothes, digestive disturbances), although a certain amount of doubt must always persist when the diagnosis rests solely on such an assumption. Investigation of this group of cases should be carried out along the lines described in the preceding paragraph. Since it will rarely be possible to obtain an electrocardiogram during a spontaneous attack of pain, and since even fairly strenuous exertion may fail to induce an attack, the influence of nitroglycerin alone may constitute the sole evidence on which a somewhat equivocal diagnosis may be made, unless one obtains indisputable evidence that paroxysmal tachycardia or hypoglycemia have been the trigger factors. *When such attacks of angina of rest do appear, and particularly if they tend to be more prolonged than usual and to occur at increasingly close intervals, the first and most important suspicion should be directed at the possibility of an impending infarction.*

### MYOCARDIAL INFARCTION

Distinction must be made between coronary thrombosis, coronary occlusion, and myocardial infarction, terms which frequently are used synonymously. Coronary occlusion may refer to any type of closure: thrombosis, embolism, or progressive narrowing to the point of closure of either an ostium or a lumen of a coronary artery.

An occlusion, whether caused by thrombosis or some other process, does not necessarily imply myocardial necrosis or infarction. Similarly, myocardial infarction may occur in the absence of coronary thrombosis or other forms of occlusion.

In a physiologic sense, angina pectoris and myocardial infarction are identical, both being expressions of the discrepancy between the nutritional supply and the energy expenditure (oxygen need) of the heart. The difference between the two conditions is one of degree: in angina pectoris the impaired blood supply to the heart is adequate to maintain the life of the myocardium, if not to prevent symptoms; in myocardial infarction the blood supply to an area of the myocardium is so compromised, usually the result of an acute coronary thrombosis or progressive coronary narrowing, that even at rest an adequate supply of oxygen cannot be obtained. In the latter case necrosis of the affected area ensues, the extent depending on the rapidity of development of the vascular obstruction, on the size of the involved artery, and, most important of all, on the effectiveness of the intercoronary collateral circulation. The event that determines the appearance of myocardial necrosis is usually an anatomic obstruction. In some instances, the additional burden may be physiologic, either an excessive demand on the heart as the result of prolonged exercise, or the protracted restriction of the blood supply from shock, or the combined effect of increased need and diminished blood supply in cases of protracted paroxysmal tachycardia. The pain in angina pectoris and myocardial infarction is similar in character, location, and reference: it is usually more severe and prolonged in myocardial infarction because the underlying disturbance of function is more severe and prolonged. However, the presence of the necrotic area in the myocardium introduces a new feature that is responsible for the additional symptoms that occur in this condition: (1) Those resulting from destruction of a functioning area of the myocardium—gallop rhythm, arrhythmias, forward failure (shock) and backward failure (dyspnea, pulmonary congestion, etc.), and lowered blood pressure; (2) those resulting from the presence of a necrotic area in the myocardium—electrocardiographic changes, acute pericarditis, mural thrombi, and subsequent embolic phe-

nomena; (3) those resulting from the absorption of certain products of tissue injury from the infarct—fever, leukocytosis, increased sedimentation rate (fig. 4).

In some cases of acute myocardial infarction there may be no history of pain. The absence

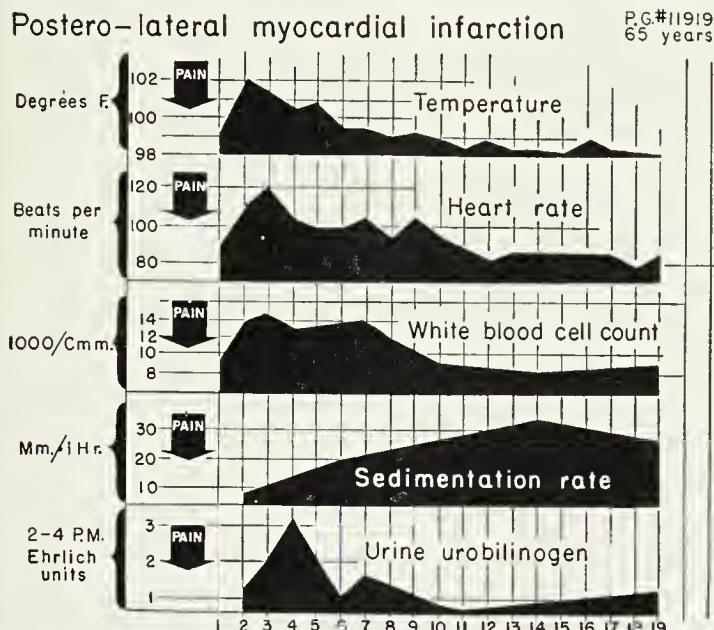


FIG. 4. Signs of tissue destruction in acute myocardial infarction. (H. H. Hecht.)

If the attack of precordial pain is followed by the changes outlined above, gross tissue destruction is present. When combined with the characteristic electrocardiographic changes, an acute myocardial infarction is present. If the latter are absent, these objective findings in the wake of chest pain will not differentiate between tissue destruction on the basis of myocardial infarction, pulmonary infarction, dissecting aneurysm of the aorta, or any other destructive process within the chest.

of pain is sometimes attributed to the relative insensitivity of the individual to pain, but this explanation cannot account for the fact that the same patient may shortly suffer from severe pain arising from another source; for example, a biliary colic or even another myocardial infarct. The afferent nerve fibers in the myocardium converge in the periarterial plexuses of the coronary arteries, thence ultimately conveyed to the upper five posterior dorsal root ganglia. It is conceivable that in the cases of painless myocardial infarction the process of necrosis may go on so slowly that the resulting sensations of pain do not arise to the level of consciousness; or when a large area of the myocardium suddenly becomes infarcted and yet is unaccompanied by pain, the periarterial plexuses of the coronary arteries, destroyed or disrupted through damage of the tiny nourishing arterial twigs arising from the pathologic coronary artery,

may be unable to mediate the sensation of pain. These explanations are speculative; the cause for the absence of pain in these cases is as yet unknown.

#### CORONARY INSUFFICIENCY

All cases of angina pectoris and myocardial infarction are due to coronary insufficiency. However, this term, or coronary failure, has been applied more specifically to a syndrome which is intermediate between angina pectoris and myocardial infarction. It should be evident that with a pathologic background such as has been described above—namely, one in which disease in the coronary arteries is being counterbalanced more or less successfully by the opening of compensating anastomotic vessels—all gradations of clinical manifestations may be encountered, from no symptom at all, or anginal pains of the mildest nature, to extensive infarction with severe prolonged pain. Coronary insufficiency is the name given to a syndrome characterized by anginal pain, longer in duration than is seen in angina pectoris, but without the appearance of any of the manifestations characteristic of myocardial necrosis. The circumstances for this condition are similar to those discussed under myocardial infarction; the more favorable outcome can be ascribed to the lesser severity or duration of the adverse factors, or to a more highly developed collateral blood supply in the myocardium. The separation from angina pectoris is an arbitrary one. Some of the longer attacks of angina occurring at rest probably should be included in the coronary insufficiency group. When prolonged seizures are separated by progressively shorter intervals, the older term "status anginosus" is applicable. This is a grave situation, for many individuals die suddenly, prior to the development of the typical signs of the infarction which usually ensues eventually.

All of these conditions (angina pectoris, coronary insufficiency, status anginosus, and myocardial infarction), which are characterized by pain resulting from myocardial anoxia, are further characterized by the likelihood of sudden death, which is usually due to the onset of ventricular fibrillation. This dramatic and tragic termination may occur at any time in the course of the disease. It is more likely to occur in those

patients who have frequent and prolonged attacks of severe pain, and especially if the seizure sets in at rest. Nevertheless, it may occur in persons who have had only the mildest symptoms. For the individual with pain due to myocardial anoxia the only certain feature of the prognosis is its uncertainty.

When we pass from a consideration of pain due to myocardial anoxia to a discussion of other types of pain in the chest, clarity gives way to confusion. The experimental observations are less numerous, more conflicting, and at times at variance with clinical impressions, which in turn are often based on inadequate studies. Since the exact mechanisms concerned in the production of the pain are in many instances unknown or disputed, the remainder of this chapter will necessarily be concerned chiefly with the purely clinical aspects of the symptom rather than with its pathogenesis.

### PERICARDITIS

Experimental studies made on man by Capps indicate that both the visceral pericardium and the internal surface of the parietal pericardium contain no pain fibers, that the only sensitive region is the lower part of the external surface of the parietal layer, and that the pain associated with inflammation of the remaining part of the pericardium actually arises in the adjacent pleura. These observations account for the fact that noninfectious pericarditis (that associated with uremia, and with myocardial infarction) is almost invariably painless, while infectious pericarditis, being nearly always accompanied by pleuritis, is usually associated with pain of the typical pleural character (i.e., aggravated by breathing, coughing, etc.). Since the central part of the diaphragm receives its sensory supply from the phrenic nerve, which arises from the middle cervical segments of the spinal cord, pain arising from the lower part of the pericardium is likely to be referred to the neck, shoulder, or even the proximal portion of the arm.

When the pericarditis is accompanied by inflammation of the pleura covering the peripheral part of the diaphragm, which is supplied by branches from the lower intercostal nerves, the pain is likely to be referred to the abdomen. However, the most common sites of pericardial

pain are the precordial or substernal regions. The important points are first, that, as a general rule, pericarditis is often an essentially painless disorder unless accompanied by pleurisy; and second, that it is only the infectious types of pericarditis which are likely to be associated with pleurisy. This generalization is often of great value in diagnosis but, like most generalizations in medicine, admits of occasional exceptions. Thus one sometimes sees patients with pericarditis of infectious origin who have a steady, dull ache, a feeling of substernal pressure, or even a sharp throbbing pain aggravated by each beat of the heart, and unrelated to respiration. As a rule, however, pain of these varieties is either entirely absent or overshadowed by the more severe stabbing pain associated with breathing, and due to the accompanying pleurisy.

Since the pain of pericarditis, unlike that of myocardial anoxia, is often accompanied by no distinguishing hallmarks, a knowledge of the more common etiologic factors, and a search for them, is often of great value in diagnosis. The diagnosis of pericarditis becomes certain only when the characteristic to-and-fro friction rub is heard but is strongly supported by a certain sequence of electrocardiographic changes consisting of elevation of S-T segments in all of the leads, followed (or preceded) within a few days by inversion of all T waves, without significant change in the QRS complexes. Unless chronic constrictive pericarditis supervenes—as is commonly the case in the tuberculous variety, but rarely with other types—the electrocardiogram usually returns to normal within a few weeks (see Chapter 31, figures 76-77).

When the pericardial friction rub and the characteristic electrocardiographic changes are absent, as may be the case in the milder instances, and especially in those which follow benign respiratory infections, pericarditis is likely to be confused with acute pleuritis. Although the distinction may be impossible, the more central location of the pain and the frequent presence of a feeling of substernal fullness should direct suspicion toward the pericardium.

In the cases of pericarditis presenting a friction rub and electrocardiographic changes, the resemblance to myocardial infarction may be striking. The latter condition usually occurs

in older patients and is more apt to be associated with evidence of congestive failure. In the case of pericarditis, there usually will be an antecedent infection, and the fever commonly antedates the pain, while the reverse relationship is found in instances of myocardial infarction. Pleuritis commonly accompanies pericarditis during the initial stages; it accompanies myocardial infarction only when a complicating pulmonary embolism has occurred, and usually a week or more after the onset. The electrocardiographic changes are usually, but not invariably, distinctive for the two conditions. In a given case these several differential points may be inconclusive, and one may have to rely entirely on the character of the pain. As a rule, the pain of pericarditis is more closely related to position, to movement—such as turning over in bed—and to swallowing than is that of myocardial infarction. The distinction between these two conditions, while occasionally difficult, is usually easy; it is important because the two diseases present totally different problems in prognosis and management.

There is a group of cases of acute pericarditis whose outstanding feature is the occurrence of pain indistinguishable from that resulting from myocardial infarction, aside from the fact that the pain is affected by respiration or change of position of body. In other words, the pain has the combined characteristics of that induced by myocardial anoxia, and of that arising in the pleura. The cause of the pain in these particular cases is a matter of great interest, and there would seem to be the following possibilities: (1) Irritation of the efferent cardiac nerve fibers, probably in the sheaths of the superficial coronary arteries, and giving rise to prolonged coronary spasm. In this case we would be dealing with a true coronary insufficiency, accounting for the acute dilatation of the heart and the shocklike features described in some of the cases; (2) irritation of the afferent nerve fibers in the periarterial plexuses, giving rise to sensations that are felt in consciousness to be identical with those brought on by myocardial anoxemia. Actual invasion of the arterial wall by the inflammatory process, with organic narrowing of the lumen, would appear to be extremely unlikely in view of the ultimate complete disappearance of all symptoms in the cases thus far reported.

## CARDIAC NEUROSIS

(Anxiety state centered around the heart)

Pain in the region of the precordium, and, more particularly, localized over the apex of the heart, may be felt by individuals in whom no evidence of heart disease can be discovered. The pain is apt to be dull, may last for hours or days, does not bear an important relationship to effort but is usually accentuated by fatigue, and is often aggravated by emotional strain or chronic ill health from any cause. Occasionally, the pain may be felt as sharp stabs occurring at irregular intervals, sometimes radiating into the arms, but again without any necessary relationship to exertion. These symptoms, sometimes associated with hyperesthesia and tenderness over the affected area, occur predominantly in nervous, high-strung persons; occasionally they seem to be associated with the excessive use of coffee or tobacco. At times the symptoms may be precipitated by concern about the heart, and may disappear promptly when emphatic reassurance has been given. These pains are due to the perception of sensations that are not felt by more placid individuals, and possibly arise from the chest wall sensitized by the beating of the heart. In favor of such a hypothesis as to the genesis of the pain are the following facts: (1) The pain is often limited to the periapical region, which receives the shock of the heart beat. (2) Tenderness localized to the region of the impulses is frequently present. (3) An exactly similar dull, periapical ache may be present in some subjects—not of neurotic makeup—with conditions such as hypertension, valvular lesions, hyperthyroidism, or even hypoglycemia, which lead to lasting or temporary increase in the force of the heart beat. Apparently two factors—the threshold of sensitivity and the force of the beat—are concerned in the production of this type of pain. An increase in either factor occasionally causes it, while an increase in both factors, such as occurs in persons with severe cardiac neurosis or in mildly hypersensitive persons with organic cardiac disease, usually produces this type of discomfort, which is especially common when cardiac neurosis becomes engrafted upon organic cardiac disease.

Ordinarily there will be little difficulty in distinguishing this type of pain from that due to any of the several forms of myocardial anoxia.

Occasionally, however, difficulties do arise. For one reason or another it may be impossible to extract from the patient a history that is clear-cut; or an apprehensive individual may deny any relationship of the chest pain to exertion, when actually fear has precluded any but the mildest effort; or the patient may state emphatically that exertion brings on a tightness in the upper substernal region, relieved by rest, and it may be almost impossible to determine whether pain or dyspnea is meant. Finally, even an obviously neurotic person with a previous cardiac neurosis may develop angina pectoris. Contrarily, individuals with angina pectoris frequently develop cardiac neurosis as the result of anxiety concerning the cardiac status.

Other aspects of cardiac neurosis are discussed in the chapters dealing with palpitation and with diseases of the heart.

#### PAIN ARISING FROM INTRATHORACIC VISCERA OTHER THAN THE HEART

##### PAIN ARISING FROM THE AORTA

###### COMPLICATIONS OF SYPHILITIC AORTITIS

It is questionable whether syphilitic aortitis uncomplicated by aortic insufficiency, closure of a coronary ostium, or aneurysm, is ever the cause of pain. If pain does occur (and vague distress has been described by some), it is so poorly defined as to have no diagnostic significance. It is a safe rule to consider uncomplicated syphilitic aortitis a painless affliction. When aortic regurgitation or closure of a coronary ostium, or both, have resulted from the aortitis, myocardial anoxia occurs in a certain rather small percentage of cases, and angina pectoris or myocardial infarction may ensue. The pain associated with aneurysm, usually saccular, is due to pressure on neighboring structures capable of giving rise to pain, practically always on bones, nerves, or root ganglions (fig. 5). In the former case the pain is boring, pressing, sometimes throbbing, and is often worse at night; in the latter case, and usually associated with the former, the pains are sharp and shooting, and segmental in distribution; in other words, they then have the qualities associated with nerve root irritation. The location and reference of the pain will depend on the affected structures. Occasionally, the pain seen in aneurysm of the

aortic arch seems to be due to irritation of the afferent nerve fibers in the outer coat of the aneurysm, for operative removal of the upper thoracic autonomic ganglions has completely relieved the pain.

#### DISSECTING ANEURYSM

This disorder is often diagnosed incorrectly during life because many patients die in the early stages, and, in those who survive, the clinical picture is likely to be either variable and bizarre, or to resemble closely that of myocardial infarction.

~~The pain is commonly substernal, continuous, and intense. Less frequently, it begins between the shoulders and in the back. In either case the pain may remain localized, or may be extended widely to head, neck, back, upper or lower extremities, or abdomen, depending on the extent of the dissection and the particular branches of the aorta affected. The pain is frequently described as "tearing," or crushing, but sometimes as constrictive.~~ In these latter cases the clinical picture may bear a striking resemblance to that produced by myocardial infarction, to which condition, in fact, the symptoms of dissecting aneurysm are commonly and erroneously attributed during life. The similarity in the pain of the two conditions is understandable: the rupture in dissecting aneurysm usually begins in the ascending part of the aorta. The pain fibers in this structure take the same course through essentially the same nerve roots as convey the pain fibers from the heart (see figure 5).

The initial bout of pain usually endures for several days. Following a period of days to months of freedom from discomfort, a second and fatal episode of pain may occur, the first attack being due to the original dissecting process, and the final episode to rupture of the outer coat of the aorta.

Repeated and careful examination of patients with dissecting aneurysm will often reveal important findings. One of them is a diastolic murmur which may repeatedly appear and disappear, and which apparently results from a functional aortic insufficiency caused by deformity of the aortic valve as the result of the dissection. Another finding consists of evanescent neurologic signs resulting from interference with the blood supply to the spinal cord as

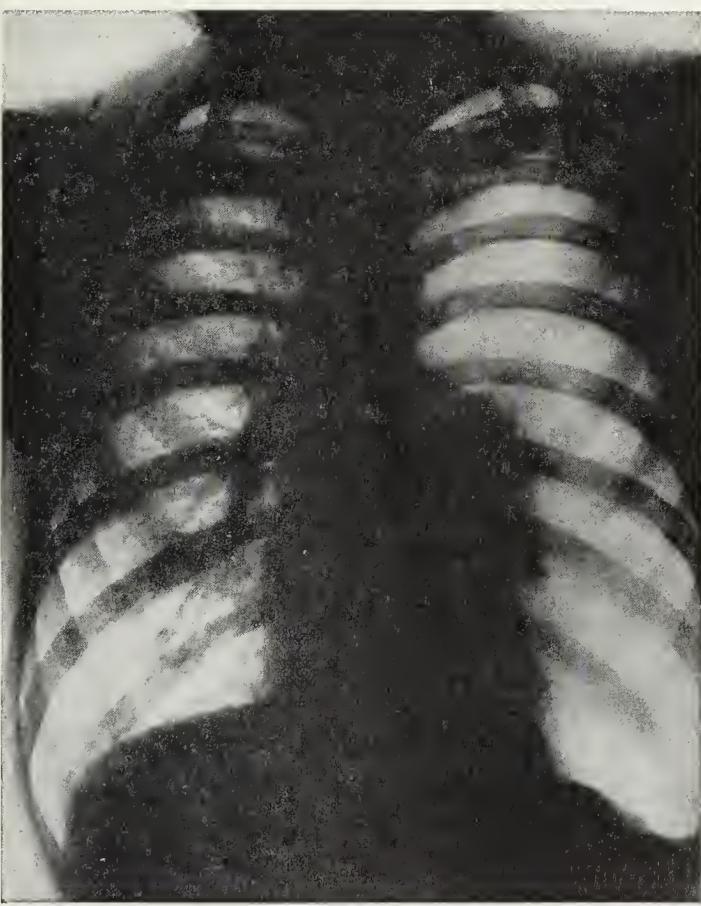
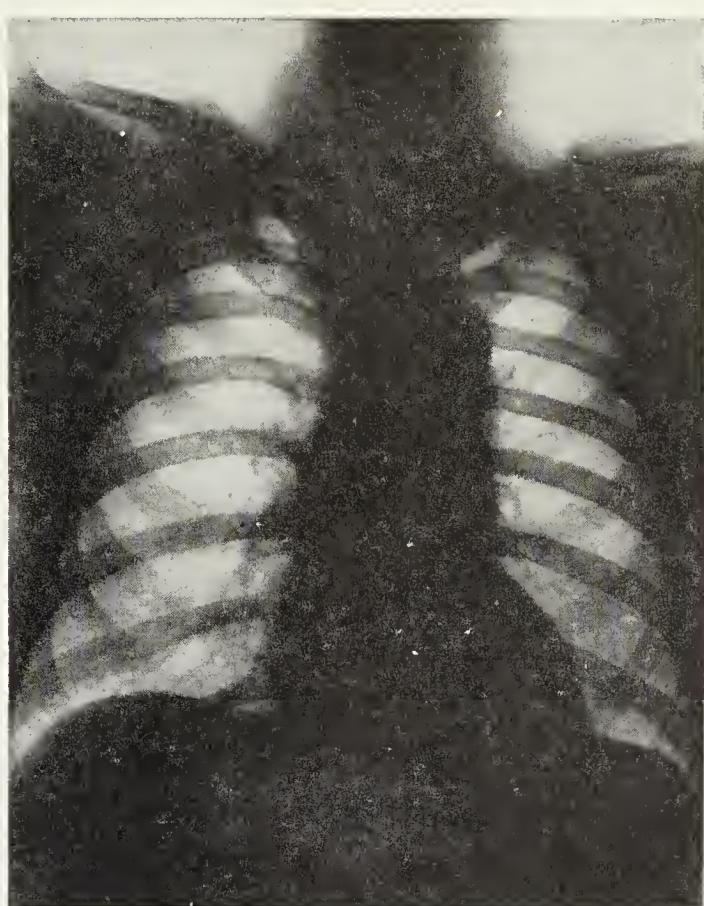
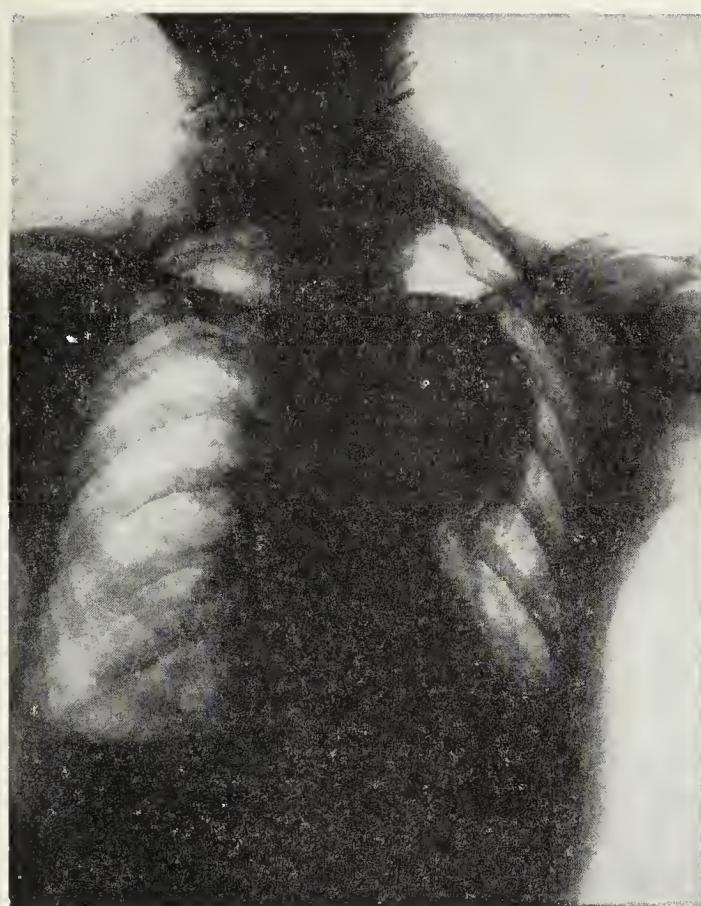


FIG. 5. X-ray films of the chest as an aid in the differential diagnosis of chest pain. (H. H. Hecht.)

Diseases of the chest wall, pulmonary infiltration, and pleurisy may be readily detected as the cause of chest pain by radiologic examination. Three of the less frequent causes of precordial distress readily detectable by x-ray examination are here illustrated: (*Top, left*) Saccular aneurysm of the arch of the aorta as the result of syphilitic aortitis in a 72-year-old housewife. (*Top, right*) Dissecting aneurysm of the aorta with diffuse widening of the entire thoracic aorta in a 52-year-old golf professional. (*Bottom, left*) Spontaneous pneumothorax with collapse of the left lung in a 28-year-old veteran. In each instance the radiologic examination provided the final answer to the complaint of pain in the chest.

the result of blockage of the mouths of intercostal or other arteries. Less commonly, systolic murmurs may appear over the back or abdomen, and rarely a friction sound, synchronous with the heart beat, and heard over the upper sternum (periaortic friction rub), may indicate seepage of blood into the superior mediastinum. These findings, plus the progressively more widespread distribution of the pain—especially in the back, abdomen, and legs—and the frequent inequality of the blood pressure in the two arms, sometimes will suffice to establish the diagnosis. In those instances in which the pain remains localized to the substernal area, and in which electrocardiographic changes develop as the result of the distortion of the coronary ostium by the dissecting process, the clinical differentiation from myocardial infarction may be impossible.

### PAIN ARISING FROM THE PULMONARY ARTERY

#### PULMONARY EMBOLISM

Pulmonary embolism may cause two types of chest pain. When a smaller embolus produces an

infarct of the lung, the pain is due to the pleuritis overlying the infarct and will, of course, have the characteristics of a pleural pain. When an embolus becomes lodged in one of the larger branches of the pulmonary artery, severe chest pain, which is indistinguishable from that due to myocardial anoxia caused by coronary artery disease, may occur. This second type of pain is thought by some to be the result of an actual diminution in the coronary flow, secondary to the profound and complicated alterations in the dynamics of the circulation. Others believe that the pain arises in the pulmonary artery itself (p. 34). In some instances the restriction of coronary circulation may actually lead to myocardial infarction, even though no gross disease of the coronary arteries can be detected. In a small percentage of cases an electrocardiographic pattern diagnostic of pulmonary embolism may be revealed (figs. 6 and 7; see also Chapter 31); in others, there may be seen changes suggestive of disturbed coronary flow but not indicative of the cause. The differential diagnosis between acute coronary occlusion and

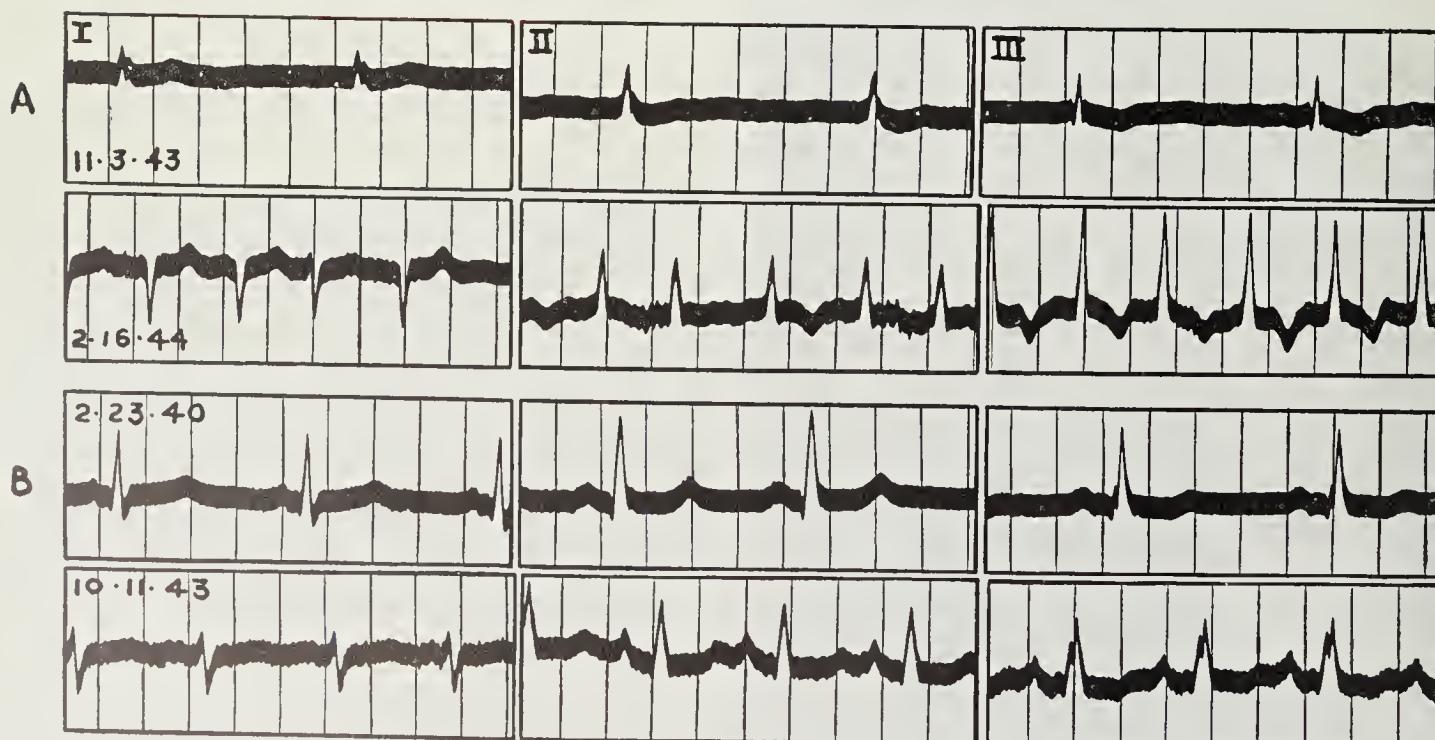


FIG. 6. The electrocardiogram in pulmonary embolism: QRS changes. (H. H. Heeht.)

~~X~~ Large pulmonary emboli may cause acute dilatation of the right ventricle ("acute cor pulmonale") with sudden onset of right bundle branch block, or striking "right axis deviation" of QRS in the electrocardiogram. These changes do not occur regularly; they are usually transitory and may last for a few hours only. When they occur, they are almost as diagnostic for pulmonary embolism as are the Q and T wave changes in myocardial infarction.

In both A and B, the sudden onset of precordial pain with signs of acute heart failure led to the provisional diagnosis of myocardial infarction. In both instances, the changes in the electrocardiogram helped to establish the correct diagnosis. In each instance, the upper records represent the standard limb leads I, II, and III before and the lower the same leads immediately after the massive pulmonary embolism.

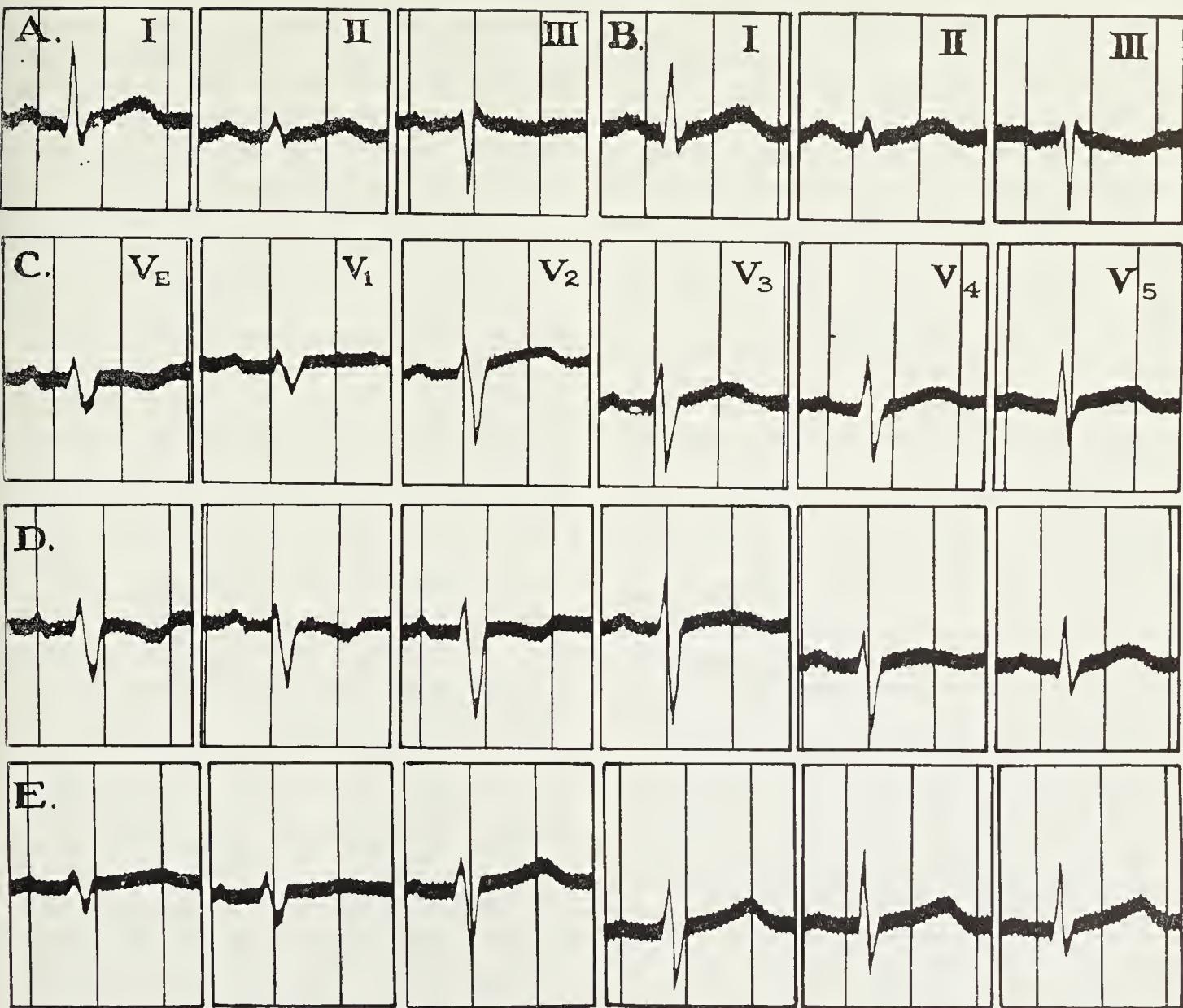


FIG. 7. The electrocardiogram in pulmonary embolism: T wave changes. (H. H. Hecht.)

Transient T wave changes following pulmonary emboli are confined to the right-sided precordial leads and/or to leads opposite the diaphragmatic surface of the heart ( $V_E$ , lead III).

The record is that of a 52-year-old veteran who suffered from repeated episodes of pulmonary emboli following a postoperative thrombophlebitis. T wave changes confined to  $V_1$ ,  $V_2$ , and  $V_E$  (a lead taken over the ensiform process) appeared within 12 hours following one of the episodes and disappeared within three days. No changes were noted in standard bipolar limb leads or in unipolar limb leads at any time.

(A) Standard limb leads before embolism. (B) Same leads 12 hours after the episode of chest pain. (C) Precordial leads before the episode but at the same time after previous infarcts (these may have accounted for the inversion of T in  $V_E$ ). They are within normal limits. (D) Twelve hours after the pulmonary infarct with terminal inversion of T in  $V_E$ ,  $V_1$ , and  $V_2$ , and flat T waves in leads  $V_3$  and  $V_4$ . (E) Almost complete clearing of all T wave changes three days after the episode.

$V_E$  and the three unipolar limb leads are not illustrated; they remained normal throughout.

massive pulmonary embolism may therefore be impossible.

The identification of the chest pain due to embolism of smaller branches, with resulting pulmonary infarction, may likewise present difficulties. Since the discomfort arises mainly from the pleura and is commonly associated with a pleural friction rub, it must be differentiated from that due to infectious pleuritis.

Indirect evidence, such as the previous presence of congestive heart failure or of a recent operation, plus evidence of phlebothrombosis in the legs (tenderness in the calf muscles, or pain in them on dorsiflexion of the foot), when coupled with such direct evidence as the presence of blood-stained sputum and a triangular shadow in the x-ray, will usually point the way toward the correct diagnosis.

### PULMONARY HYPERTENSION

Another type of pain which probably arises from the pulmonary artery is observed occasionally in patients with mitral stenosis, congenital cardiac disorder, bronchial asthma, and other conditions which produce pulmonary hypertension. This pain is indistinguishable from that of myocardial anoxia in regard to location, quality, and intensity. It may be precipitated by muscular effort which elevates the pulmonary arterial pressure in such subjects, and may be relieved by rest. When the duration is brief it resembles angina pectoris; the more prolonged attacks mimic myocardial infarction. The distinguishing hallmarks of this pain, which has been called "hypercyanotic angina," but might perhaps more appropriately be designated as "pulmonary hypertensive pain," are (1) its frequency in persons with disorders which hinder the pulmonary circulation; (2) the tendency toward wheezing and cyanosis during the seizures; (3) the occurrence of right axis deviation and alterations in the T waves in leads II and III; (4) the ineffectiveness of nitroglycerin as compared to the effectiveness of drugs which relieve the wheezing.

### PAIN ARISING FROM THE LUNGS, BRONCHI, PLEURA, AND MEDIASTINUM

#### PLEURITIS

The important clinical principles concerning pleural pain were elucidated by the studies of Capps, on man. His observations indicated that the visceral pleura, like the lungs, apparently possesses no pain fibers, but that the parietal pleura is very sensitive to pain, which, because of the many spinal cord segments which enter into the sensory nerve supply of the pleura, may be felt in any region between the lower neck and the lower abdomen. Recent studies showing that pleural pain may be relieved by the administration of calcium gluconate, or of curare, suggest that spasm of the muscles of the chest wall may be an important factor in the production of the pain.

In the case of pain arising from the pleura, as in that due to myocardial anoxia, it is the character and behavior of the pain rather than its location which is of diagnostic value. The characteristics of pleural pain are its sharp,

superficial, lancinating or "catchy" quality, its aggravation by deep inspiration and by coughing, its tendency to disappear entirely when the breath is held in the expiratory position, and its tendency to be decidedly worse in certain recumbent positions than in others.

Chronic adherent pleuritis usually produces little or no pain and is best recognized by the use of x-ray. Acute pleuritis causes no abnormalities in the x-ray unless there be an effusion, and produces only one physical sign—the characteristic friction rub. Even this valuable sign is absent in a large percentage of the cases, and thus the recognition of pleuritis frequently depends entirely on the character of the pain. Even so, one should bear in mind that not only pleuritis and pleuropericarditis but also certain other conditions, such as myocardial infarction and herniation of the stomach through an esophageal hiatus, may at times produce a pain that is aggravated by breathing, and that many pains arising from the spine are precipitated by coughing. However, any pain in the chest, abdomen, or lower neck, which is sharp in character, induced by breathing, and completely relieved momentarily by holding the breath, should be considered as of pleural origin until proved otherwise.

*Epidemic pleurodynia*, a relatively rare infectious disease apparently due to a virus, represents a special type of pleural pain. It should be suspected when an individual presents the combination of severe pain of pleural type in the lower chest and abdomen, in association with headache and fever.

The bronchi rarely give rise to severe pain. A mild sensation of substernal burning aggravated by breathing is often present in individuals with bronchitis. A mild feeling of substernal pressure is, likewise, commonly present, but it is uncertain whether this arises in the bronchi or in the swollen mediastinal nodes. Both of these types of discomfort may be present in persons with bronchogenic carcinoma, but are likely to be overshadowed by the more severe pain due to involvement of the pleura and mediastinum.

#### PNEUMOTHORAX

The pain in this condition is sharp, localized over the site at which the pneumothorax takes

place, and often of short duration, the severity depending on the acuteness of onset and the extent of the extravasation of air between the pleural membranes. The pain is due to the irritation of the parietal pleura and is usually transitory because the pleural surfaces are separated by the interposition of the air. The episode of acute pain may be followed by a vague sense of fullness which probably is due to tension in the mediastinal structures. While it persists, the acute pain has the typical qualities of that arising from the pleura, having no distinguishing quality other than the tendency toward short duration. The diagnosis is therefore made by the demonstration of the characteristic physical signs and radiographic evidence of air in the pleural cavity (see figure 5).

#### PAIN ARISING FROM THE MEDIASTINUM

##### *Mediastinal Emphysema*

In this rather uncommon condition, severe chest pain may be encountered, sometimes very similar to that caused by myocardial infarction, at other times sharper and more superficial, and influenced by respiration. Either type of pain may be affected by change in position of the body. The character of the pain would suggest that the first pain is due to irritation of mediastinal structures whose afferent nerves take essentially the same course and enter the same posterior roots as do the afferent fibers from the heart; the second type of pain is clearly due to pleural irritation. The recognition of this condition will depend on the detection of subcutaneous emphysema or pneumothorax, or on the detection of a peculiar crunching or crackling sound, synchronous with the heart beat, along the left border of the heart.

Although the *mediastinal lymph nodes* are frequently the seat of disease, they do not commonly give rise to characteristic discomfort. Acute bronchitis is sometimes accompanied by a mild feeling of fullness behind the upper sternum, and, since this sensation resembles that felt in persons with lymphomatous involvement of the mediastinum, it probably is induced by swelling of the nodes. Occasionally, such an infection may spread to the pericardium or pleura, but in such instances any discomfort arising in the lymph nodes is overshadowed by

the more severe and sharp pain arising from these regions.

Severe and even violent pain occurs in the mediastinum when there is rupture of the aorta or esophagus. In such instances a constant sense of constriction behind the sternum is accompanied by sharp pain due to irritation of the mediastinal pleura, and having all the qualities of pleural pain.

#### PAIN ARISING FROM THE ESOPHAGUS

Although there is no unanimity of opinion regarding details of the sensory innervation of the esophagus, it is generally agreed that it is derived from the vagus and the sympathetic system (probably the inferior cervical and upper nine thoracic autonomic ganglia). This extensive innervation explains the variety of localization and the wide reference of the pain sometimes seen in disorders of the esophagus. Clinical and experimental observations point to esophageal tension as the primary stimulus for the production of pain in this organ. The pain is commonly behind the sternum, especially the lower part, is usually described as being constrictive or burning in quality, and is commonly precipitated by swallowing. The discomfort may so closely resemble the pain of angina pectoris or myocardial infarction, particularly when due to esophageal spasm, as to present perplexing problems of diagnosis. Differentiation from cardiac pain will depend chiefly on the absence of relationship to exertion, the association with eating, the difficulty of swallowing, the radiologic investigations made preferably during the attack of pain, reproduction of the pain under observation when possible, and electrocardiographic and esophagoscopic studies.

#### HEARTBURN

The most common type of discomfort arising from the esophagus is "heartburn," a slightly uncomfortable feeling of warmth felt behind the lower sternum, commonly associated with belching, and apparently due to reflex constriction of the lower part of the esophagus brought about by the regurgitation of gastric contents. Spasm of the esophagus is another common condition, the discomfort usually being a mild retrosternal feeling of constriction, but occasionally being severe and radiating to the left shoulder. Al-

though nitroglycerin may give relief, atropine usually causes more striking benefit, and this fact may be of considerable value in differentiating esophageal from cardiac pain.

Less common causes of discomfort arising in the esophagus include carcinoma, diverticulum, peptic ulcer, and (rarely) varices. In such instances the story of the retrosternal location, plus the relationship of the discomfort to the act of swallowing, will suggest the esophagus as the responsible organ, but the exact nature of the disease process will be recognized not by the character of the pain but by the result of the radiologic and esophagoscopic examinations.

#### PAIN REFERRED TO THE CHEST FROM ABDOMINAL ORGANS

If acute pleuritis be omitted from consideration, about 10 to 20 per cent of the patients with recurrent attacks of pain in the left side of the chest will be found, on careful analysis, to be suffering from discomfort arising in the abdominal rather than the thoracic cavity. Although the exact nerve pathways are not known, clinical experience teaches us that any of the upper abdominal organs may at times give rise to pain in the chest, and this is especially true of disorders of the stomach. *Aerophagia* and *pylorospasm* commonly produce a mild sense of fullness in the lower substernal region, the precordium, or, more frequently, the left anterior part of the chest. Discomfort from these disorders occurs especially in emotional individuals, is usually mild, is commonly relieved by belching, tends to be prevented by atropine, is often accompanied by palpitation, and can usually be reproduced by inflation of the stomach with air.

Less frequent but more dramatic is the discomfort associated with abnormal configuration of the fundus of the stomach, including herniation through the esophageal hiatus of the diaphragm, "cascade" deformity, and diverticulum. The pain commonly radiates from the lower substernal area to the shoulder, is constrictive in character, mild to very severe, may or may not be related to eating and belching, is often worse in the recumbent posture, and tends to be aggravated by alcohol and by emotional upsets as well as by breathing. One especially characteristic feature of such pain is the tendency to come in paroxysms lasting a minute or two, with

one or more minutes of relief between the seizures. The resemblance of the discomfort to that associated with myocardial anoxia may be striking, but repeated radiographic examination of the stomach, especially if carried out in various positions and while the pain is present, will usually identify the cause.

Peptic ulcer may give rise to mild substernal or precordial pain which is probably induced by the associated pylorospasm, as atropine commonly gives relief. Although perforated ulcer may produce pain resembling that of myocardial infarction, the two conditions will rarely be confused if the history is carefully taken, and if one bears in mind the differences between the manifestations of peripheral circulatory failure and acute cardiac failure (see Chapter 14). More puzzling are those exceptional instances of gallbladder disease in which the pain radiates anteriorly and toward the left shoulder rather than posteriorly and to the right. Whether, in such instances, the pain is actually referred from the gallbladder or is induced by reflex constriction of the coronary arteries remains unknown. The confusion is enhanced by the fact that disorders of the gallbladder and of the coronary arteries frequently coexist.

Acute pancreatitis may lead to severe circulatory collapse which can readily be mistaken for that due to myocardial infarction. In most instances the distribution of the pain, which in pancreatitis usually spreads from the epigastrium to the back of the lower part of the left side of the chest, is of diagnostic value, and, when taken with the characteristic elevation of the blood amylase, serves to differentiate the two conditions.

Pain in the spleen, which usually results from acute infarction, has the typical sharp "catching" quality of pleural pain, bears the same relationship to respiratory movements, and is commonly associated with a friction rub. The differentiation—not always easy—is based on the location, which is in the region of the left lower ribs, anteriorly and laterally—an unusual location for pleural pain.

The splenic flexure of the colon may be the site of pain which is usually cramplike, but may be sharp and related to breathing. The discomfort resembles that arising in the stomach, in location and character, but tends to be relieved by bowel movements and by the expulsion of flatus.

In doubtful instances the decision as to whether chest pain is arising from the splenic flexure usually can be made by determining whether the discomfort can be exactly reproduced by inflation of the colon with air through a tube inserted into the rectum. (Experimental studies on man have shown that while colon pain, in general, is referred to the lower abdomen, pain arising from either flexure tends to be felt at a higher level—upper abdomen or lower chest. The occasional relationship of splenic flexure pain to breathing is probably due to inspiratory compression of the distended flexure by the descent of the diaphragm.)

### PAIN ARISING IN THE CHEST WALL

The only disorder of the skin which is likely to produce pain that can be confused with that arising from the intrathoracic viscera is herpes zoster. Here the superficial and burning quality of the pain, its segmental distribution, and the associated cutaneous hyperesthesia should lead to the suspicion of the true cause, even prior to the appearance of the characteristic eruption.

Painful disorders of the ribs are usually due to trauma, in which case the pain may actually arise in the pleura, due to injury by a fracture, or to neoplasm, such pain being steady, progressive, boring or throbbing, and worse at night. Less frequently, an acute pain in the anterior part of the chest may result from displacement of a costal cartilage which slips upward over the adjacent rib. In such an instance the pain is sharp, aggravated by standing erect or raising the arms, associated with sharply localized tenderness, and at times with an audible click when the loosened cartilage is moved.

Numerous disorders of the spine, including arthritis, metastatic neoplasm, tuberculosis, osteomyelitis, and cord tumors, may cause pain in the chest. The discomfort is usually severe in the back but may radiate around the entire chest, producing either a sensation of a constricting band or sharp lancinating pain. Relationship to posture is usually striking, the pain often becoming slowly worse in a given position, and then being alleviated temporarily. Although breathing is usually without effect, sudden respiratory movements, such as coughing and sneezing, tend to cause pronounced aggravation. When the vertebral bodies are affected, the pain tends to be worse at night and throbbing in

character. Associated with the more severe pain arising in the spine there is commonly a dull soreness and stiffness in the muscles of the back.

A type of pain which may be especially puzzling is that resulting from pressure of the anterior scalenus muscle on the branches of the brachial plexus. This pain is commonly felt in the shoulder or arm, and less frequently in the upper pectoral region. It may be sharp or constrictive, and is increased by lifting a weight or pulling the arm downward. Since the pain is commonly noted when the subject walks while carrying a heavy object—such as a suitcase—and since the pain may vanish quickly when this activity ceases, the condition may be readily confused with angina pectoris. Patients suffering from this condition—the scalenus anticus syndrome—experience dramatic temporary relief when this muscle is injected with procaine. In some, but not all, instances a cervical rib is present, and there may be various circulatory changes in the arm due to pressure of the ribs on the subclavian vessels.

Pain may occur in the pectoral, deltoid, or other muscles of the shoulder girdle or arm. Confusion with angina pectoris may arise from the fact that the pain is intensified by walking. However, the pain starts with the first step, and if the subject walks without swinging the arms it does not develop. Furthermore, the discomfort is found to be related to specific movements of specific parts and not to exertion in general, and there is likely to be local tenderness in the affected muscle. Similar considerations apply to discomfort arising from joints and bursae.

“Intercostal neuritis” is an expression commonly applied to a multitude of chest pains of different origins. Certainly a true neuritis in the sense of an inflammation of an intercostal nerve, or even in the broader sense of a toxic or degenerative change in the nerve, is rarely the cause of chest pain. Practically always “intercostal neuritis” will be found to refer to a pain having the quality of pain arising in the chest wall—i.e., pain arising in relation to specific movements rather than pain in relation to general exertion.

Perhaps the most confusing fact in relation to pain arising in the skeletal tissues of the chest is that disturbances in the coronary circulation

frequently lead to reflex changes in muscle tone—and occasionally in blood supply—in the region of the shoulder. Thus pain may arise in the skeletal tissues when the primary disease process is in the heart. It probably represents a form of causalgia, or reflex sympathetic dystrophy. As a rule, this occurs after a myocardial infarction, but occasionally a patient with mild angina pectoris may have this "coronary shoulder pain" which is related to local movements of the arm, accompanied by local tenderness, etc. Under such circumstances the presence of the more annoying, but less important, skeletal pain may distract attention from the less obvious but more serious pain resulting from myocardial anoxia. Serious mistakes will be avoided if a meticulous search—including a detailed history, observation of the response to effort, and electrocardiograms before and after exercise—is made for angina pectoris in all middle-aged and elderly persons complaining of pain, stiffness, or soreness in the region of the left shoulder.

### DIFFERENTIAL DIAGNOSIS

The proper interpretation of the cause of obscure chest pain depends, first of all, upon suspecting the true cause, and, second, upon demonstrating its presence by some objective procedure. If one is to avoid subjecting every patient to a veritable barrage of special procedures—many of them unnecessary in a given patient—it is essential that one gain the clue as to the one or two most likely conditions from the story of the pain.

When a given attack of pain lasts for only a few minutes, the diagnosis is not usually too difficult, but confusion is more apt to arise when the pain endures for several hours or longer. The purpose of the discussion to follow is to attempt to clarify such instances, and also to summarize some of the more important points which have been emphasized in this chapter.

The heart receives pain fibers from the upper four pairs of thoracic ganglions, as the aorta probably does also. These same ganglions contribute to the more extensive afferent supply received by the esophagus. After entering the cord by the posterior nerve roots, their ascent in the cord and their central terminations are, presumably, identical; and, as is true of all pain

arising in the viscera, the pain is poorly localized and more or less diffuse. Hence, it should not be surprising that these structures, supplied by afferent fibers that have a final common pathway, should give rise to pains that are frequently similar, and sometimes identical. (The problem is not so clear in the case of the esophagus, for it has been demonstrated that even after all the thoracic sympathetic ganglions have been extirpated, distention of the esophagus may still cause substernal pain. It has been assumed that accessory afferent pathways, either through the vagus or through fibers running along the esophagus and entering the cervical cord, mediate pain. Certainly, accessory pathways must be postulated for the ~~X~~ production of pain of anginal distribution by disorders of the gallbladder, stomach, or colon, unless it is assumed that this pain is due solely to reflex coronary constriction.) The clinical application of this knowledge indicates that neither the location, quality, nor reference of a chest pain arising from these organs can denote with certainty the origin or nature of the underlying disorder. This information can be gained only from careful study of the circumstances calling forth the pain, and the antecedent, contemporary, and subsequent history of the development of symptoms and signs. Thus a preceding history of exertional angina will point to coronary insufficiency or myocardial infarction as the cause for a similar but prolonged attack of chest pain, as will also the appearance of anginal pain during an attack of paroxysmal tachycardia or hypoglycemia, or following severe hemorrhage. ~~X~~ The wide distribution of the pain, particularly the extension to the back, the occasional neurologic symptoms and inequality of the pulses, the appearance of an evanescent diastolic murmur, and the absence of electrocardiographic manifestations of cardiac infarction in an individual who has previously enjoyed good health, and whose pain was brought on in the performance of some strenuous exertion, will denote the development of a dissecting aneurysm. The combination of severe substernal or precordial pain, plus pleural pain, together with the demonstration of a crunching sound along the left border of the heart, and of subcutaneous emphysema or pneumothorax, will indicate the presence of mediastinal emphysema. The sudden development of chest pain, either pleural in character (small embolus) or con-

strictive and resembling that of myocardial anoxia (large embolus), in a patient recuperating from an operation or confined to bed for whatever reason, for a number of days, should bring up the possibility of pulmonary embolism. A constant boring pain should lead to the search for aneurysm. Substernal pains associated with the act of eating, or with difficulties of swallowing, will suggest some disorder of the esophagus; and a similar pain after a full meal, and occurring particularly as the patient takes the ~~recumbent~~ posture, should recall a hiatus hernia. Chest pains clearly unrelated to exertion, and appearing in conjunction with digestive disturbances, will lead first to the thought of some abdominal disorder. But here the problem becomes more difficult, for reflex coronary constriction may actually be producing true angina pectoris in an individual already suffering from coronary sclerosis. If the patient also gives a history of anginal pain on exertion, the interpretation of the similar pain, sometimes prolonged, occurring in conjunction with the abdominal symptom, will be clarified. If, however, the pain cannot be induced by exertion, the pain does not respond promptly to nitroglycerin, and no significant alterations in the electrocardiogram during the attack of pain can be revealed, it is probably safe to ascribe the pain to the abdominal disorder.

In any case of chest pain, it will be the first duty of the physician to think of the heart as the source of the trouble. In a fairly high percentage of cases, careful attention to the details of the history and examination, securing frequent electrocardiograms and interpreting them cautiously, plus the additional laboratory tests and radiologic examinations that would be called for by the problems inherent in the case, will make possible an accurate diagnosis either incriminating or exonerating the heart. The greatest difficulty in this regard will arise in patients who have suddenly developed severe chest pain, and who are so ill that careful study is not possible; or who are seen so early in the illness that insufficient time has elapsed for pathognomonic signs to have appeared; or who, suffering from any of the less common causes of severe chest pain, such as pulmonary embolism, dissecting aneurysm, mediastinal emphysema, or hiatus hernia, will be considered victims of myocardial infarction, because the other pos-

sibilities have not been entertained. Difficulties will also be encountered in patients who have no angina on exertion but who suffer from attacks of prolonged angina of rest ("coronary insufficiency") due to paroxysmal tachycardia, hypoglycemia, or impending infarction, especially when the attacks do not come under the immediate observation of the physician.

If careful study absolves the heart with reasonable assurance, and if at the same time the possibilities of pulmonary embolism, dissecting aneurysm, or mediastinal emphysema have been investigated and rejected, attention will then be directed to the digestive tract as the cause of trouble.

It is important to bear in mind that a number of these conditions that may be confused with myocardial infarction may exhibit elevation of temperature, leukocytosis, and elevation of the sedimentation rate (pulmonary embolism, dissecting aneurysm, biliary colic). It is even more essential to know that electrocardiographic changes may result from a variety of causes too numerous to mention. Pain alone, of extracardiac origin, may induce these changes. Hence, abnormalities of the electrocardiogram, even if known to occur during the attack of pain, must be considered diagnostic of myocardial infarction only if accompanied by unequivocal and characteristic alterations in the initial ventricular complex (see Chapter 31, figures 78-79). Even if the patient is known to suffer from angina pectoris or to have had a previous infarction, some unrelated extracardiac malady may exist concurrently. Combinations such as coronary disease with gallbladder disease or esophagospasm are not uncommon. The electrocardiogram is an invaluable aid in the investigation of chest pain, but once again must be repeated the trite admonition that it cannot replace a judicious assessment of *all* the evidence bearing on the problem.

It is impossible to lay down a systematic program for the investigation of chest pain. The special tests that will be called for will be determined by the tentative deductions that will have been drawn from a careful analysis of the history: serial electrocardiograms, x-rays of the chest, esophagus, gastrointestinal tract, gallbladder, and spine will be made according as the circumstances dictate. When the conditions

prevent the physician from seeing the patient during a spontaneous attack, the reproduction of the pain may be attempted—usually a simple matter when the question of angina pectoris has arisen, more difficult but nevertheless necessary when clarification of certain of the other obscure pains is concerned.

At the risk of tiresome repetition, it should be stated again that the cause of chest pain in a given patient will rarely be identified unless it is first suspected; that the proper suspicion usually will arise only from a meticulous history; and that often the most important feature in the story is not the location, quality, or intensity of the pain, but its behavior in relation to the various body functions, such as position, excretion, breathing, eating, etc. It is only by means of a careful history that the physician can secure an Ariadne's thread to guide him through the confusing labyrinth of chest pain.

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## 4

# Acute Abdominal Pain and Ileus

C. A. Moyer

### Abdominal Pain

- Classification of Abdominal Pain
- Abdominal Pain of Parenchymatous Origin
- Abdominal Pain of Neurogenic or Central Origin
- Ileus
  - Mechanical Ileus
  - Reflex Ileus
  - Metabolic Ileus

### ABDOMINAL PAIN

Abdominal pain may be defined as a consciousness of distress in the abdomen. Under certain conditions this manifests itself as indigestion, which will be considered later. It may have

a parenchymatous, metabolic, or neurogenic origin. The following etiologic classification, while not complete, includes the more important causes of this symptom.

### CLASSIFICATION OF ABDOMINAL PAIN

#### I. Parenchymatous:

- A. Pain referred to the abdomen from extra-abdominal disorders (i.e., from thorax, spine, or genitalia)
- B. Pain having its origin within the abdomen:

1. Incident to disturbances of function or obstruction of hollow organs

bowl  
bile ducts  
ureter  
bladder  
pancreatic duct

2. Incident to peritoneal inflammation:

a. Chemical

gastric juice  
pancreatic juice  
urine  
bile

b. Bacterial

3. Incident to disturbances in blood supply:

a. Pressure or torsional occlusion

volvulus  
strangulated hernias  
twisted  
pedunculated cysts  
uterine fibroids

b. Embolism and thrombosis

arterial  
venous

c. "Inflammatory" (e.g., visceral angiitis)

4. Incident to disruption of a viscus (e.g., rupture of a viscus or tearing apart of arterial walls)

5. Incident to an increase in tension upon supporting elements:

a. Traction on mesenteries

b. Rapid swelling of capsules (e.g., congested liver, carcinomatous lymph nodes)

c. Rapid separations of leaves of mesenteries

new growths  
rupture of vessels

6. Incident to disease of muscle:

a. Traumatic myositis

b. Infectious myositis

viral  
bacterial  
parasitic

#### II. Metabolic:

##### A. Endogenous:

1. Toxic (uremia, diabetic coma, porphyria)
2. Allergic

##### B. Exogenous:

1. Toxic (e.g., lead poisoning)
2. Biologic (e.g., bite of the black widow spider)

#### III. Central or Neurogenic:

##### A. Organic:

1. Lesions of the central nervous system (postapoplectic pain)
2. Root pain (including the "lightning" pain of tabes dorsalis)
3. Causalgia

##### B. Ideogenous ("mind pain," "psychogenic pain")

Many of the general manifestations of abdominal pain are the same as those associated with pain in other parts of the body—namely, changes in facial expression, body carriage, and physical activity, a reduction in the care of the person, and changes in the rate of the pulse and respiration. However, certain manifestations are rather intimately related to abdominal pain of parenchymatous origin. These include avoidance reactions directed toward emptying the alimentary tract, such as sticking the finger down the throat to induce vomiting, repeated attempts to evacuate the bowel at stool, the self-administration of enemas and purgatives. Flexion of the thighs, retching, spasm of the abdominal muscles, and abdominal distention are other signs that are commonly associated with pain of the parenchymatous type.

The differentiation of abdominal pain is difficult. The location of the pain, its type (colicky, steady, boring), its mode of onset, its rate of change in intensity, its relationship to eating and to evacuation of bowel and bladder, are historically important in the determination of cause. The degree and location of muscle spasm, changes in the pattern of breathing, the location of tenderness to percussion and to steady increase in pressure, the threshold of counter pain necessary to remove abdominal pain from consciousness,

and the determination of changes in cutaneous sensitivity are signs of importance in the differentiation of abdominal pain.

### ABDOMINAL PAIN OF PARENCHYMATOUS ORIGIN

**Referred abdominal pain** is the enigma of the surgeon, for he recognizes that the lower thoracic cavity and the upper abdomen are neurologically and lymphatically one unit. For example, early acute lobar pneumonia, with basilar pleurisy, may be attended by severe abdominal pain and a degree of "spasm" of the abdominal muscles which is so intense as to lead one to think that a duodenal ulcer has perforated, or that the gallbladder has ruptured and peritonitis is present. To make matters more confusing, the abdominal pain of pneumonia may be present before any physical or roentgenologic signs of pneumonia are detectable. Conversely, acute cholangitis and acute subphrenic abscesses are often associated with pleuritic pain in the lower right chest, and signs of fluid or atelectasis of the lower lobe of the lung. Coronary occlusive disease and acute cholecystitis, with cystic duct obstruction, may also be mistaken one for the other.

The differentiation of referred abdominal pain from that arising within the abdominal cavity may depend solely upon the course that the illness takes during a brief period of careful observation. However, a tentative opinion of the probable anatomic location of the primary difficulty can often be made from the elucidation of a few clinical signs.

Abdominal pain referred from within the chest is usually associated with alterations in breathing, lag, and restriction of motion of the lower thoracic segment, that are much more apparent than those associated with pain of intraabdominal origin. In addition, pain that accompanies intraabdominal inflammatory processes (exclusive of those limited to the lesser omental cavity) is generally associated with spasm of the abdominal muscles that *does not* perceptibly relax during the inspiratory phase of the respiratory cycle; but the spasm occasioned with the referred type does relax during inspiration. Evidently the reciprocal inhibition of the abdominal muscles, which are expiratory muscles, that normally takes place during inspiration still occurs with referred abdominal pain but does not occur with that of peritonitis. Another point of difference

that may be of help is that steady, gentle pressure over the painful area does not materially increase, and may actually relieve, the pain if it is referred, but generally increases it if it is of intraabdominal inflammatory origin.

It is especially important that referred and intraabdominal inflammatory pain be differentiated, because the latter often indicates immediate surgical intervention. Intrathoracic diseases more commonly associated with abdominal pain are: lobar pneumonia, coronary occlusive disease, infectious pericarditis, and "cardiospasm." The routine careful search for specific clinical signs of their existence will often lead to the correct inference as to the origin of pain that appears superficially to be of abdominal origin. However, it is well to remember that diseases may be coexistent, and the existence of intrathoracic or intraabdominal diseases before the acute disease develops, even though it may be "asymptomatic," may result in unusual areas of reference of the acute pain. For example: A painless healed abdominal incision, especially if it is recent, often becomes the point of reference for pain arising from widely separated organs within the abdomen. Though it has not as yet been proved, it is thought that the same principle may explain the peculiar references of pain with acute gallbladder disease to the left shoulder, if coronary occlusive disease exists; and the radiation of the pain of myocardial infarction to the epigastrium or right upper quadrant of the abdomen, if preexisting, though asymptomatic, gallbladder or duodenal disease is present.

Referred pain arising from the testis is acutely intensified by light testicular pressure, and that arising from the seminal vesicle is usually relieved by expression of its contents. That arising from vertebral disease has the characteristics of root pain.

*The commonest causes of abdominal pain having their origins within that cavity are disturbances in the function of hollow organs, intraabdominal inflammation, and increase in tension of supporting elements.*

**Pain associated with disturbances in function of hollow organs** is, at least initially, intermittent or colicky. It is generally associated with definite organic disease, but may occasionally accompany variations in physiologic function without visible organic disease. Anyone who has observed the

terrific colic of acute coccal food poisoning or who, having made a diagnosis of acute intestinal obstruction, has had the misfortune of performing a celiotomy upon an individual who is actually suffering from porphyria, and has seen the unbelievable contortions performed by the intestine, is convinced that severe colic can be associated solely with changes in physiologic function.

Parenchymatous pain incident to disturbances in the function of various hollow organs has certain relatively specific areas of reference. That associated with obstruction of the cystic duct or distention of the gallbladder is referred most commonly to the epigastrium, then to the right posterior chest about the scapula, and occasionally to the left lower quadrant of the abdomen. Sudden common bile duct or pancreatic duct obstruction by stone produces pain that is felt in the epigastrium and in the upper lumbar region of the back. The colicky pain of midgut obstructive origin, or, in other words, terminal duodenal, small intestinal, appendiceal, ascending and proximal transverse colonic obstructive origin, is generally supraumbilical or circaumbilical. That associated with lesions in the flexures of the colon is felt over these areas. Obstructive lesions of the lower descending and sigmoid colon produce pain that is felt most often in the left iliac region and over the sacrum.

Obstruction of the ureter from below the ureteropelvic junction to its intravesical portion is productive of pain that is initially felt directly over the point of obstruction, but after spasm of lumbar and flank muscles develops, the pain becomes diffuse and tends to cover the flanks. Acute occlusion of the intravesicular portion of the ureter, and of the proximal urethra, tends to produce pain which is referred to the shaft of the penis, the scrotum, and the inner surface of the thigh in the male, to the inner surface of the thigh in the female, and to the suprapubic regions of both sexes.

Rapid distention of the bladder is productive of suprapubic pain. Obstruction of the ureteropelvic junction is associated with pain in the costovertebral angle.

**Pain incident to an inflammatory process involving a parietal peritoneal surface** is located over the area involved, and is steady and aching in character. The rate of its development and its intensity are dependent upon the mass and char-

acter of the chemical substances which impinge upon a given surface per unit of time. For example, a cubic centimeter of highly acid sterile gastric juice, or a cubic centimeter of sterile alkaline pancreatic juice (which, in addition to their acidity and alkalinity, are enzymatically potent) in the peritoneum is immediately productive of much more intense inflammation and pain than is a cubic centimeter of bacteria-laden, neutral, enzymatically impotent liquid feces from the ascending colon.

Ultimately, as the bacteria multiply and elaborate irritants, the peritoneal surface over which the organisms spread becomes severely inflamed and painful. The differentiation between inflammatory processes of bacterial chemical and body chemical origin is primarily dependent upon the analysis of progression of the inflammation or pain (fig. 8).

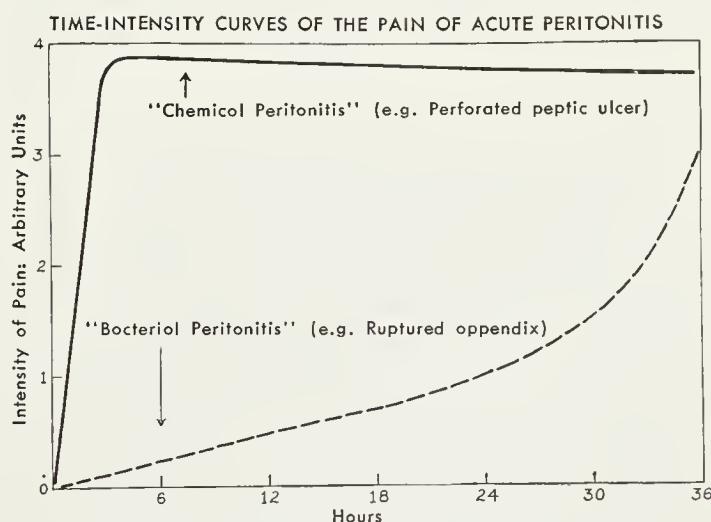


FIG. 8. The time-intensity curve of pain due to peritonitis depends on the underlying cause. When enzymatic digestion of the peritoneum is responsible, the pain rapidly reaches a maximal degree of intensity. When bacterial inflammation is responsible, the progression is much slower and is apparently related to the rate of bacterial growth.

Another factor that must be considered in the analysis of the severity of the pain that accompanies an inflammatory process is the rate of change in the intensity of the stimulus. If the rate of change in the intensity of a stimulus is sufficiently slow, no sensation of pain will be felt, even though a very intense, widespread inflammatory reaction be present (e.g., tuberculous peritonitis); if the rate of change is very rapid, the pain is intense (e.g., ruptured duodenal ulcers). In general, the intensity of pain is more intimately related to the rate of change in

strength of stimulus than it is to the area to which the stimulus is applied.

The location and extent of tonic muscle spasm, which usually occurs with peritonitis, is fundamentally dependent upon the surface area involved in the process. The intensity of the spasm is usually related directly to the rate of development of the inflammation, and is related inversely to the functional integrity of the central nervous system. The latter relationship is especially important. A severely ill, or a dying, man will not show spasm of the abdominal muscles, even though his stomach or gallbladder ruptures. Degenerated psychotic (schizophrenic) patients, those suffering from advanced Parkinson's disease and from extensive multiple sclerosis, have been observed in whom the acute rupture of a viscus (gallbladder or duodenum) with widespread generalized peritonitis has been unattended by any significant degree of muscle spasm.

*The pain incident to inflammation is aggravated by pressure on the abdomen.*

Abdominal pain that attends vascular occlusive disease is characteristically rapid in onset, and agonizing, if the process is at all extensive. It tends to be constant and diffuse. If it is not complicated by coexistent inflammatory pain, the tonic spasm of muscles is much less in relation to the severity of the pain than is the muscle spasm that is associated with an acute peritoneal inflammation.

The pain that attends the rupture of a viscus (excepting those containing potent chemicals) is a sudden, sharp, terrifying pain that is quickly over. The pains of rupture of the gravid uterus, or the spleen, or the distended, obstructed appendix are of this type.

**The pain that frequently is associated with an increase in the tension upon supporting elements of organs (capsules, ligaments, and mesentery)** tends to be steady and aching in character, increased by muscular activity, and relieved by rest, and may vary considerably with change of posture. It may be absent in the morning, following a well-slept night, but increases gradually during the activities of the day. It is not well localized; it tends to be circumumbilical and suprumbilical if the organ involved lies in the abdominal cavity, and infraumbilical, suprapubic, and in the low-back region if the organ involved

is located in the pelvis. Gentle percussion with the closed fist or pressure over the organ involved aggravates this type of pain. The area of tenderness to percussion shifts with position if the organ involved is mobile (e.g., lymph nodes in the mesentery). Abdominal muscle spasm is usually minimal if present at all.

Abdominal pain associated with generalized myositis of infectious origin mimics that of pain of intraabdominal inflammatory origin. It is constant, aching, aggravated by movement and pressure, and is associated with tonic muscle spasm. The main differential point between the pain of myositis and the pain of peritoneal inflammation is the presence, in the former, of tenderness and spasm of muscle masses that are not innervated by the nerves supplying the peritoneum, and, in the latter, limitation of muscle spasm and tenderness to their areas of distribution.

Abdominal pain of "metabolic" origin may mimic all other types, and its recognition depends upon the constant awareness on the part of the doctor that it may simulate early small intestinal obstruction, appendicitis, cholecystitis, ruptured ulcer, etc.

The abdominal pain with sickle-cell anemia tends to migrate, and the areas of tenderness likewise tend to shift within brief periods of time (one to three hours).

That associated with diabetes and uremia has no specific characteristics.

The bite of the black widow spider is productive of severe pain and rigidity, not only in the abdominal muscles, but also in the long muscles of the back (sacrospinalis), a region rarely affected by pain of intraabdominal origin.

The abdominal crisis of chronic porphyria mimics acute intestinal obstruction, and is characteristically attended by signs of increased peristaltic activity that are unusually prominent.

The pain of lead colic has no specific characteristics.

Ileus, or obstruction of the intestine, may accompany all types of abdominal pain. Its relationship to pain is discussed later.

#### ABDOMINAL PAIN OF NEUROGENIC OR CENTRAL ORIGIN

Organic central pain may be diffuse (postaplectic) or localized (cord or root pains). Cord

and root pains tend to have a sudden onset (lightning pains) and a lancinating character, and are often limited to a few neural segments. They have no consistent relationship to eating. Muscle spasm may be well developed but is not particularly increased by pressure. Changes in nerve thresholds are common (hyperesthesia—hypesthesia). Distention of the abdomen is uncommon and persistent changes in breathing are not seen often.

**Causalgia (Peripheral Type).** This quality of pain is usually limited to areas of distribution of peripheral nerves that have been partially severed or have partially regenerated after complete severance or pressure block. Its quality is variable; usually the person cannot describe it concisely; it is most troublesome to the patient during the periods of rest.

In persons with causalgic pain the respiration and muscle tonus are normal; the threshold of counter pain necessary to remove abdominal causalgic pain from consciousness is low; the light touch of a pinpoint to the forehead is frequently enough. The geographic distribution of cutaneous pain points is grossly altered in the painful area. The points are very irregularly spaced, with frequent gaps of a centimeter between them. In fact, disturbance in pain-point distribution may be the only significant clue that the pain being suffered is causalgic. In general, peripheral causalgia seems to be fundamentally related to a change in the relationships of the various cutaneous sensory stimuli that simultaneously impinge upon the central nervous system.

For example: Feeling a rough surface is not a painful experience, but it may be if the ulnar or median nerves are partially severed. The recognition that a surface is rough is dependent upon a pattern of stimuli arising in touch, pressure, and pain endings. Unequal interference with the receptive capacity of various sensory endings or fibers so changes the central appreciation of feeling a rough surface as to make it distressful to the individual. The painful sensations that accompany the stepping on a "sleeping" foot are similar to causalgia, and the differential disturbances of various peripheral sensory components are relatively easily demonstrable.

**Psychogenic pain** is characterized by indefiniteness of onset, diffuseness of location, and casual definition of type, with little or no relationship to meals or evacuation. Generally, irregularly cyclic muscle spasms may be felt, and

many bizarre types of change in the character of breathing may be seen. The commonest type of change in breathing is a restriction of the depth of inspiration without accentuation of the speed of expiration. The expiratory accessory muscles of respiration may be tonically (not rhythmically) active. If generalized abdominal muscle spasm is present, the abdomen will be protuberant in the lateral view, and normal or narrow in the anterior view. Generally speaking, no persistent localized point of tenderness will be present excepting when the abdomen is scarred. The physical signs of central ideogenous pain can be obliterated by the suppression of consciousness (sleep or "Pentothal,"  $N_2O$  "analgesia"), or by inducing a powerful stimulation of breathing with 10 per cent carbon dioxide.

The foregoing chapter has been concerned, in the main, with the more severe types of abdominal pain. The milder types of abdominal discomfort will be considered in a later chapter dealing with indigestion.

## ILEUS

A diminution in the rate of progress of intestinal contents through the gut is the fundamental sign of the acute and chronic forms of ileus. Intestinal obstruction may be classified etiologically as follows:

1. Mechanical
  - a. Intrinsic
  - b. Extrinsic
- with or without interference with volume flow of blood to the intestine
2. Reflex
3. Metabolic ("paralytic")

The reflex and metabolic types have been generally grouped under a single heading, "paralytic," by reason of the fact that with them peristaltic activity is reduced or abolished. However, the efficacy of the treatment of ileus depends primarily upon the physician's ability to make the correct etiologic diagnosis, and consequently the tendency to place reflex and metabolic types of ileus under a single heading, such as paralytic, obviates definitive treatment.

Regardless of the etiologic type of ileus, the physiologic consequences thereof are qualitatively comparable within certain limits. The disturbances in physiologic regulation that accompany ileus are predominantly respiratory,

circulatory, and hydrodynamic in the early phases, and nutritional and toxic (infection and tissue injury) in the later phases. More specifically:

1. Respiratory exchange becomes progressively limited as abdominal distention progresses and asphyxia develops. It may be said that intestinal obstruction garrotes a man by seizing him by the belly. The mechanism of the choking is probably identical with that of a vertical burial up to the neck in sand.

2. The rate of the pulse increases and hypotension tends to occur. These changes can be produced quickly to some extent by distention of isolated segments of the intestine (closed duodenal loop syndrome) or of the stomach (acute gastric dilatation) before appreciable changes in fluid distribution occur. Therefore, they are partially, at least, of reflex origin.

3. Extracellular fluid collects within the lumen of the intestine because absorption is remarkably reduced by a relatively little distention, while the rate of excretion is affected little. This functionally deprives the rest of the body of extracellular fluid, even though it is still within the person. It is obvious that vomitus represents extraneous loss of extracellular fluid.

In addition to the almost invariable extracellular fluid volume deficit, many compositional disturbances tend to occur—namely: base bicarbonate excesses and defects, excesses of beta-hydroxybutyric and acetoacetic anions, chloride deficits, hypokaliemia, and hypocalcemia. The osmolar concentration, when disturbed, is usually reduced. In addition to the sequestration of extracellular fluid within the lumen of the gut and the extraneous loss thereof through vomiting, blood cells are sequestered in the vessels contained within the hyperemic obstructed bowel. This increase in the vascular bed of the obstructed gut constitutes a functional loss of blood in so far as the rest of the body is concerned. These hydrodynamic and hemic aberrations contribute greatly toward the inception of peripheral circulatory failure.

4. Starvation inevitably occurs to some extent with ileus, and becomes a major problem in dealing with long-standing progressive partial obstructions of the stomach (peptic ulcer, cancer), small intestine (regional stenosing enteritis) and large intestine (cancer).

5. The toxic consequences of ileus are, in the

main, caused by wet gangrene of the bowel wall with leakage of bacteria into the peritoneal cavity per diapedesis early, and per rhexis later. The gangrene is a consequence of sufficient distention of the intestine to impair circulation to local areas, or of direct occlusion of vessels by torsion, thrombosis, or external pressure. The more extensive the death of bowel and the leakage of bacteria, the more pronounced the general signs of tissue destruction will tend to be (fever, leukocytosis, general ileus).

## MECHANICAL ILEUS

### Classification of Mechanical Ileus:

1. *Intrinsic* (causative agents)
  - a. Foreign bodies in the intestine and appendix (gallstones, fecoliths, worms, bezoars, bones, etc.)
  - b. Tumors of the large and small intestine
  - c. Intussusception (invagination of bowel)
  - d. Inflammatory disease of the bowel (segmental enteritis)
  - e. Segmental spasticity
  - f. Impacted feces
2. *Extrinsic* (causative agents)
  - a. Hernia (external and internal)
  - b. Peritoneal bands
  - c. Tumors
  - d. Torsion

The signs and symptoms of mechanical ileus vary somewhat with the site of the obstruction, the causative agent, the rate of development of obstruction, and the degree of reduction of blood flow through the intestinal vessels. In general, the local signs of mechanical ileus are: intestinal colic, hyperperistalsis, vomiting, obstipation, and abdominal distention.

The pain of mechanical intestinal obstruction is colicky; that is to say, it waxes and wanes. The pain and the hyperperistalsis tend to increase and decrease concomitantly, and the sufferer may say that the pain is at its worst when gas is heard moving within the abdomen. The synchronization of the ascent and descent of the pain with the same phases of peristaltic activity constitutes intestinal colic, and is a most important diagnostic point.

The pain of obstruction of the small intestine, the appendix, the ascending colon, and the right half of the transverse colon is generally located

between the ensiform cartilage and the region immediately about the umbilicus; that of the left half of the transverse colon, the descending colon, and sigmoid is usually in the infraumbilical and left iliac regions. Rectal and lower sigmoidal obstructions, in addition to the above locations, often have an associated sacral locus. Obstructions at the colonic flexures usually have an immediate local position in addition to the areas of reference previously described. (Additional clinical features of the pain have been discussed.)

These general rules regarding the location of the pain are by no means absolute and may apply *only when there are no surgical scars on the abdomen*, because the reference of pain of intraabdominal disease, regardless of anatomic site, tends to be toward abdominal scars, more especially if they have been made recently or are poorly healed (incisional hernia) even though old.

The frequency with which the colics follow one another depends to some extent upon the location of the obstruction. The highest frequency (every one to three minutes) is seen with obstruction of the jejunum, and the least frequent with obstructions of the sigmoid (every five minutes to three hours).

*The appearance of a continuous pain* at any time, with or without cessation of the colic, heralds the appearance of peritonitis or the occlusion of mesenteric vessels (reduction in blood flow). With the onset of peritonitis, peristalsis may be increased for a time before it diminishes; with the onset of vascular occlusion, peristalsis and colic tend to diminish soon, especially if any appreciable segment of the intestine becomes anoxic.

Hyperperistalsis is a general accompaniment of the colicky pains. In addition, the peristaltic sounds are high-pitched and often have a tinkling quality. The high pitch of the sounds is due to the high tension of the gas and fluid within the gut. The intestine behaves acoustically like a kettle-drum; an increase in the tension of the drum-head raises the note.

In general, the higher in the intestine the obstruction is located the more frequently does vomiting occur. It is practically a universal accompaniment of jejunal obstruction, and very closely follows the onset of pain. It is an unusual sign with sigmoidal obstruction, excepting after a long period of obstipation. The vomiting does

not relieve the colics of mechanical intestinal obstruction, whereas it does relieve the distress of pyloric obstruction. Vomiting of a dark-brown or feculant vomitus is not an invariable accompaniment of mechanical ileus. It is a late sign, and is a sign of approaching death.

The degree of obstipation varies with the completeness of the obstruction. The intrinsic type is, for a time, usually intermittent and incomplete. This is especially true of obstruction by polypoid tumors of the small bowel, by gallstones, and by bezoars.

Distention is also a variable sign; it tends to be often indiscernible with high jejunal obstruction and closed-loop obstruction, especially when the stomach has been emptied by vomiting or intubation. In general, the lower the point of obstruction, the greater will be the meteorism.

If the distention of the mechanically obstructed intestine becomes sufficiently great, the intestinal colics and hyperperistalsis cease, active vomiting may stop and effortless regurgitation ensue, and generalized abdominal tenderness without reflex muscle spasm appears. These events presage the development of intestinal failure or the decompensational phase of mechanical intestinal obstruction. When celiotomy is performed during this stage of mechanical intestinal obstruction, one observes in these instances during the performance of the celiotomy, a bowel wall of such thinness that fluid levels within the bowel can readily be seen, that peristaltic activity is absent although spinal anesthesia extending up to the fifth dorsal spinal segment is employed, which practically rules out reflex inhibition of the intestine, and even gentle manipulation of the bowel is followed by local separations of the serosa. This gut is so acutely overloaded that it cannot contract functionally, and may be said to be acutely decompensated.

It is obvious that decompensational ileus is usually an advanced state of mechanical ileus; however, it does complicate the other types. A rapid or a slow continuous entry of air into the intestinal tract through the esophagus while the various etiologic factors involved in ileus are operative predisposes to the development of the decompensational phase of ileus. The rapid ingress of air into the gut, excepting by actually swallowing it, is mainly due to abnormalities of breathing. Grunting or sighing respiration tends to force a part of the air, which gains access to

the esophagus during inspiration, into the stomach. This process of gastric aspiration of air may be very rapid; as much as 3 liters of air have been observed to gain access to the gut in 20 minutes, without a single act of swallowing having been made. Grunting and sighing breathing may be associated with psychogenic disorders and with many illnesses other than those afflicting the abdominal cavity; for instance, spontaneous pneumothorax, fractured ribs, pneumonia, pleurisy, myocardial infarction, acidosis, apoplexy, and pulmonary infarction. These illnesses are frequently associated with meteorism and obstipation. Whether the ileus accompanying these illnesses is fundamentally metabolic or reflex, or a combination thereof, is as yet unknown.

The signs and symptoms of the decompensational phase of ileus vary with the chronicity of the process and the segments of the gastrointestinal tract which are involved.

Acute idiopathic gastric dilatation at times may be attended with little or no pain, and at others severe constant epigastric distress is suffered. Frequent, almost effortless<sup>1</sup> regurgitation of a foul, nonfeculant, "coffee-ground" vomitus is the rule. Generally, little or no nausea is felt. The area of gastric tympany in the dorsal or sitting position rises into the left chest, and succession splashes usually are readily produced. The systemic signs are often those of fulminating peripheral circulatory and respiratory failure. A rapid rise in temperature may occur terminally. Acute gastric dilatation is often quickly fatal; as little as three or four hours of acute gastric dilatation has resulted in death. The decompositional phase of ileus is a state from which recovery cannot be attained except by an adequate and prolonged period of suctional decompression through tubes.

Therapeutically, the *most important* diagnostic decision to be reached regarding mechanical obstruction of the small bowel is whether the blood flow to the bowel is sufficiently impaired by high intraluminal tension or by the occlusion of large vessels to result in gangrene. Obstruction without dangerous interference with blood flow is *not* an immediate surgical emergency, whereas that with interference with flow is.

If all mechanical obstructions of the small bowel are treated as immediate surgical emer-

gencies—that is to say that celiotomy is performed as soon as possible after the diagnosis is made, regardless of the amount of abdominal distention that is present—the operative and postoperative mortality is very high, about 50 per cent. On the other hand, if some time is taken to correct fluid imbalances and to deflate the obstructed bowel as much as possible within a reasonable period of time when blood flow to the gut is not embarrassed before celiotomy is performed, the danger to life is relatively little. However, if *interference* to the blood flow is present, temporization beyond the time necessary to combat peripheral circulatory failure increases the mortality rate.

The differentiation of simple mechanical ileus from mechanical ileus with interference with blood flow is often a difficult matter. The important correlatives are shown in table 1.

The development of the symptom-sign complex of a so-called "typical case of obstructive appendicitis" illustrates the transition from a simple mechanical obstruction of the appendix to a mechanical ileus of that organ, with interference with blood flow.

#### Signs and Symptoms of Obstructive Appendicitis:

##### SIMPLE OBSTRUCTIVE PHASE (EARLY):

1. Epigastric or perumbilical colicky ("green-apple") bellyache.
2. Nausea and vomiting.
3. Spasm of the voluntary type.
4. Tenderness is relatively mild over tip of cecum and appendix.
5. Fever up to 99.4° F.

##### OBSTRUCTIVE WITH INTERFERENCE WITH BLOOD FLOW PHASE (LATER THAN ABOVE):

1. Pain, continuous in region of appendix, usually right lower abdominal quadrant.
2. Tenderness increases and covers a larger area.
3. Reflex muscle spasm is present.
4. Body temperature rises; leukocyte count increases.
5. The area of tenderness and spasm increases rapidly if a fecal leak develops, and is not limited in distribution.

<sup>1</sup> The vomitus flows out of the mouth as a slow stream, without retching. The regurgitation often can be induced by shifting the patient's position in bed.

Table 1

	<i>Simple Mechanical Ileus</i>	<i>Mechanical Ileus with Obstruction to Blood Flow</i>
Pain	Colicky	Colicky with a continuous basic pain or an initial colicky period followed by subsidence of the colic coinciding with the appearance of a continuous pain. The continuous pain is often excruciating
Abdominal tenderness	Usually absent early between colics, but later may appear, especially if the distention of the gut is large. It is relatively mild, generalized, and it increases slowly in severity	Tenderness is present. It tends to be localized early, but spreads rapidly if generalized peritonitis develops. It increases rapidly in severity
Localized mass "Muscle spasm"	None "Voluntary" spasm is usually present to some extent with the pains, but alternate contractions and relaxation of the abdominal muscles, with forced expiration and inspiration, respectively, are generally apparent between colics, and consequently "reflex" or inflammatory spasm may be said to be absent. That is to say, as long as the reciprocal inhibition of the abdominal muscles during inspiration is readily discernible, spasm, if present, is probably voluntary	Very frequently present In addition to "voluntary spasm," "reflex" or inflammatory spasm* is present locally or generally, depending upon the extent of the peritonitis
"Constitutional" signs of tissue damage: Fever, pulse rate, leukocytosis	Not elevated beyond the levels to be expected from the disturbances in fluid balance and asphyxia that exist	Elevated beyond that to be expected from disturbance in fluid balance and asphyxia that exist

\* Reciprocal inhibition of the abdominal expiratory muscles is abolished.

### REFLEX ILEUS

Reflex ileus or inhibitory ileus is generally, though inappropriately, termed paralytic ileus. It frequently attends the acute obstruction of hollow organs such as the appendix, the cystic duct, the common duct, the pancreatic duct, the ureters, the bladder, and the seminal vesicles. It is associated with torsional strangulation of ovarian cysts, uterine myomas, and the testes, and compression strangulation of masses of the omentum or preperitoneal fat in hernial sacs. It is also met in conjunction with acute pancreatitis, peritonitis, retroperitoneal hematomas and abscesses, fracture dislocations of the dorsal and lumbar spines, and manual manipulation of the intestine. Actually, the bowel is not paralyzed because peristaltic movements can be reinstated readily, at least temporarily, by spinal anesthesia or splanchnic nerve block; and, experimentally, it can be obviated by previous bilateral splanchnicectomy.<sup>2</sup> The several pathways involved in

the reflex inhibition of peristalsis consist of varied somatic afferents, and visceral afferents that course mainly in the thoracolumbar sympathetic fiber chains until they gain access to the dorsal roots, and visceral efferent fibers that are contained within the thoracolumbar motor systems.

The differentiation of simple reflex inhibition ileus from mechanical obstruction, especially in its "decompensational" phase, is often impossible when a good history cannot be obtained.

The pains complained of by an individual who suffers incidentally from reflex inhibitory ileus obviously can be protean in character, location, and intensity, because of the multiplicity of etiologic factors.

Generally, an extreme fulminant meteorism is present with reflex inhibitory ileus, and the entire intestinal tract tends to be involved. However, occasionally the distention may be limited to the stomach, to short segments of the small bowel, or to the small bowel and proximal colon. When these unusual distributions occur they may provide the basis for an erroneous diagnosis, especially when the scout x-ray examination of the abdomen is relied upon as the primary diagnostic measure.

<sup>2</sup> The reflex ileus caused by manual manipulation of the intestine cannot be prevented by blocking or sectioning the splanchnic nerves alone; the celiac ganglion needs to be rendered functionless in addition to the splanchnic nerves.

When vomiting occurs it is frequently regurgitant or relatively effortless, and is often not attended or preceded by nausea. An unquenchable thirst often is suffered by those afflicted, and if they are permitted to drink they will do so without satiation, because little or none of the water drunk gets out of the intestine except as vomitus. It is obvious that these people actually tend to drink themselves to death, for the water they drink removes salt from the body and increases the distention.

Generalized abdominal tenderness is present with the higher grades of meteorism, and intestinal colic is an infrequent complaint except during the phase of recovery. Postoperative "gas pains," other than those due to actual mechanical obstruction, are the colics of the recovery phase of reflex inhibitory ileus.

Intestinal colic is differentiated from other colics by the coincidence of variations of peristaltic activity with the pain if the colic is of intestinal origin, and lack of coincidence thereof if the colic is ureteral or biliary.

During the development and sustenance of reflex inhibitory ileus, peristaltic sounds are feeble and widely spaced, if they are heard at all. The sounds of the peristaltic rush are absent. If the distention of the intestine is sufficient to tense the abdominal muscles, breath sounds and heart sounds may be heard clearly over the whole abdomen. This is also true of decompensational and mechanical ileus, if meteorism is great.

### METABOLIC ILEUS

Metabolic ileus is of two types: the overactive or spastic, and the paralytic. The former is met with in individuals suffering from lead intoxication (lead colic), acute porphyria, and uremia. The paralytic form attends acute severe anoxia (as in pneumonia); potassium deficit, especially when it is associated with alkalosis; and severe sodium deficit.

The symptoms and signs of the spastic form are the same as those which are associated with mechanical ileus, because the spasticity tends to be local and therefore serves functionally as a mechanical block. It may therefore be placed in the mechanical obstructive group as well as in the metabolic. Since the essential treatment of

mechanical ileus, excepting the spastic type, is surgical, and that of metabolic is medical, the inclusion of spastic ileus of metabolic origin in the metabolic group rather than in the mechanical may serve therapy better.

The abdominal symptoms and signs of paralytic metabolic ileus are essentially the same as those of the reflex inhibitory type.

It is apparent indirectly in the preceding discussion that one, two, three, or four forms of ileus may exist simultaneously or consecutively in the same individual. For example: A loop of small bowel becomes incarcerated in a hernial sac, and subsequently the lumen of the efferent limb becomes obstructed; the loop distends with gas and fluid and the afferent limb becomes occluded proximally. Reflex inhibitory ileus then tends to be added to the simple mechanical form; the distention of the loop with fluid progresses and the blood flow to it is stopped. Anoxic paralytic ileus of the now strangulated piece of intestine supervenes, the strangulated intestinal wall begins to die, and bacteria are extruded into the hernial sac and from thence into the peritoneal cavity; and the ensuing peritonitis adds to the reflex inhibitory ileus. While the above events have been transpiring, extracellular fluid has been collecting in the proximal bowel and is being permanently lost through vomiting. A sodium deficit is thereby produced, which adds a metabolic factor to the ileus. An operation is now performed and the gangrenous bowel lying within the hernial sac is resected and the continuity of the gut is restored by an anastomosis. We then wonder why normal peristaltic activity is not resumed immediately, for the mechanical factors and the primary inflammatory reflex factor have been removed. However, after the operation, reflex inhibitory ileus due to handling of the intestine and to the bacterial peritonitis exists, as well as a metabolic ileus due to the sodium deficit, that can hardly be completely corrected preoperatively. These factors tend to maintain the ileus for varying lengths of time, depending upon the rates of disappearance or correction of the underlying causes—reflex and metabolic. Occasionally, the sequence of events is reversed. An individual who for years has had hernia which has always been easily reducible and has not produced obstructive symptoms, contracts pleurisy, or develops cardiac decompensation. An inhibitory or metabolic ileus appears. The intestine

in the hernial sac becomes distended with fluid and gas, and as a consequence thereof the hernia becomes irreducible and mechanical obstruction of the intestine is produced; this then may be followed by strangulation, etc.

The differential diagnosis of ileus is often difficult; this is the reason for the number of unsuspected mechanical obstructions of the intestine that are found during post-mortem examinations. Obstipation, in varying degrees, is a fundamental complaint or sign of ileus. It is to be understood that passage of small amounts of feces, gas, mucus, and stained odoriferous fluid which may be tinged with blood, is compatible with the incomplete and even the complete mechanical intestinal obstruction, because the bowel below the point of obstruction is still physiologically functional, and it is capable of passing its contents and secretions along. An enema will often be completely expelled in the presence of complete mechanical obstruction of the small bowel for the same reason, and consequently the response to an enema cannot be employed as a functional test for mechanical ileus.

The actual observation of intestinal eolic in conjunction with obstipation is sufficient evidence to make a tentative diagnosis of mechanical intestinal obstruction, even though the other signs of intestinal obstruction are not present, roentgenographically or physically.

The presence of varying degrees of obstipation, distention, or vomiting in the absence of intestinal eolic makes the establishment of a specific diagnosis of the type of ileus present much more difficult, because mechanical obstruction of the "closed loop" type, in which peristalsis tends to be reflexly inhibited, mechanical obstruction in its decompensated phase, reflex ileus, paralytic metabolic ileus, or combinations thereof, may then exist.

The diagnosis of any illness depends upon the collection and the interpretation of evidence. In order to collect the evidence about ileus well, the examiner must know the characteristics of diseases causing ileus. It is obvious, from the previous discussion, that the examiner's knowledge must be very broad. After the evidence is collected the integration thereof is the next step. This should be directed toward answering the following questions:

- Where is the primary trouble located?
- What are the pathologic processes present?

What are the disturbances in physiologic regulation that exist?

The employment of x-rays will often answer the question: Where is the primary trouble located? "Scout films" (anteroposterior upright and a lateral prone) and the barium enema are the two technics of greatest value in ileus. Barium should never be given by mouth in the face of ileus, except when provisions have been made for its immediate and complete evacuation at the highest point of obstruction, because the packing of barium above the point of a partial obstruction often makes it complete and renders definitive surgery much more hazardous and difficult. This is especially true in regard to partial obstructions of the lower ileum and colon.

If, on the scout films, all the small bowel and colon (including the rectosigmoid) contain air, the ileus that exists is *not* likely to be mechanical. The limitation of gaseous distention to the right and proximal left parts of the colon is highly suggestive of mechanical obstruction in the sigmoid or rectum. The limitation of distention to the small bowel is indicative of mechanical obstruction of the small bowel. The finding of an isolated loop of distended gut is suggestive of a "closed-loop" obstruction or a volvulus.

The interpretation of the films must be integrated into the clinical picture.

Excluding the manifold specific processes that give rise to the reflex and metabolic obstructions, a tentative answer as to the nature of the pathologic process present within the abdominal cavity of an individual suffering from ileus can be made from the integration of a relatively few factors garnered from the history and the gross physical findings. The association of constant pain and local tenderness without reflex muscle spasm is indicative of interference with the blood flow to an organ prior to the onset of parietal peritonitis. The combination of constant pain, abdominal tenderness, and reflex muscle spasm is indicative of peritonitis, with or without interference with blood flow to an organ. Colicky pain without tenderness between colies, without reflex abdominal spasm, but with peristalsis coinciding with the pains, signifies mechanical intestinal obstruction without significant interference with blood flow.

When pain has not played a prominent part, the distended silent abdomen, without spasm of the abdominal muscles, makes one suspect the

presence of a metabolic ileus. The silent distended abdomen associated with pain that is not "intestinal colic" denotes the presence of a reflex ileus. The distended, silent, spastic, tender abdomen is very good presumptive evidence that peritonitis exists, and that the reflex inhibitory ileus present is of inflammatory origin.

The integration of the physical findings relative to the abdomen *must be preceded* by a neurologic examination of sufficient extent to ascertain whether or not the function of the central nervous system, and especially the spinal cord, is normal. In the presence of peripheral vascular failure (shock), cord function often decreases with remarkable rapidity, so that even when a fulminating peritonitis exists *no abdominal muscle spasm* obtains, and only slight tenderness is felt even with rough palpation.

The signs of intraabdominal disease in the psychotic, those suffering from the varied organic ills of the spinal cord, brain, and peripheral nerves (such as neuritis due to diabetes, beri-beri, or plumbism), are often bizarre, and are usually meager in relation to the intraabdominal disease present, when they are compared with those found with similar diseases in individuals with normal mental reactions and with fully functional nervous systems.

The question as to what disturbances in physiologic regulation are present with ileus can be adequately answered by determining:

1. The state of the peripheral circulation.
2. The status of the volume (Chapter 28) and the composition of extracellular fluid, and the concentration of electrolytes (Chapter 29) in it.
3. The severity of the general anoxia, if any exists.
4. The nutritional state of the individual.

The determination of the above factors is necessary for the formulation of supportive therapy.

**Treatment.** The definitive treatment of mechanical ileus is surgical. The employment of suction methods as the ultimate form of treatment for mechanical ileus is applicable only for that form which occurs during acute peritonitis.

The definitive treatment of reflex ileus varies with its cause.

The specific treatment of metabolic ileus needs no comment.

The treatment of the decompensational phase

of ileus varies with its associations; in general, suction decompression of the gut is of primary importance.

Although the definite therapy of ileus varies, *decompression of the distended intestine is of greatest importance* in the prevention of death and the reduction of morbidity from all forms. To allow the development of and, worse, the continuance of meteorism in individuals suffering from fractured ribs, broken backs, hyperextension casts, pneumonia, pulmonary infarction, biliary and renal colic, and myocardial infarction, is as reprehensible as to allow the same in an individual suffering from mechanical obstruction of the bowel. The disturbances in physiologic regulation that attend the meteorism, and subsequent vomiting of all forms of ileus, are qualitatively similar (see above). The person having pneumonia is more anoxic because of the intestinal distention; he suffers a functional loss of blood into intestinal vessels that he can ill afford; he loses extracellular fluid, which certainly cannot be of great benefit to him, and the reflexly induced cardiovascular changes incident to the meteorisms do not lighten his cardiac load. This type of reasoning can be generally applied to any illness that is associated with intestinal distention.

Because a large part of the gas within the bowel, in all forms of ileus, gains access to the gut through the esophagus, the use of gastroduodenal suction under those circumstances that are conducive to ileus will serve to prevent the development of meteorism.

A short Levin tube is an adequate instrument through which suction can be applied in order to relieve gastric dilatation, and to prevent ingress of air into the bowel; it is also effective in decompressing the small intestine if its tip is passed into the duodenum. However, the long intestinal tubes, when they can be passed, are often more effective in relieving small bowel distention than the short tubes are. It must be remembered that, when the long tube has gained access to the small bowel, gastric dilatation and distention of the proximal intestine can occur behind it. When this takes place, productive vomiting recurs or persists. In this case, two tubes must be inserted, one into the stomach to keep it empty of air and fluid, and the other into the intestine to deflate it.

Suctional decompression of the intestine can be aided by the administration of oxygen through

a Boothby-Lovelace mask. This procedure depletes the body of its nitrogen (the inspired gas is oxygen; the expired gas is a mixture of  $O_2 + N_2 + HOH + CO_2$ ), and thereby reduces the volume of gas within the gut by an amount equal to the volume of nitrogen contained within it.

The employment of high enemas, a tradition in the treatment of ileus, often does more harm than good. If the obstruction is complete and of mechanical origin, the enema accomplishes nothing if it is expelled, and adds to the distention if it is retained. When enemas are administered to those who suffer reflex, metabolic, and decompensational ileus, they are frequently completely retained. However, an irritating soapsuds or turpentine enema may make even a reflexly inhibited gut writhe for a while before it again becomes apathetic and redistends. This makes favorable nursing notes but rarely accomplishes anything for the patient. Functional gastric or duodenal suction surely serves those who suffer ileus better than enemas.

The use of pituitary extract as an "intestinal stimulant" is mentioned only to be condemned. In the writer's experience it has caused pain without producing coördinate intestinal activity; in two instances severe angina pectoris was induced by it—but the ileus remained.

Physostigmine and "Urecholine" are occasionally very effective in the treatment of post-operative inhibitory ileus. However, it is safer to

stimulate a distended intestine by tube decompression than it is to whip it to life with stimulant drugs.

The supportive treatment of ileus is dictated by the disturbances in physiologic regulation that may be present (see p. 52). These principles are covered in the appropriate chapters dealing with anoxia, circulatory failure, and disturbances in the volume or composition of the body fluids (Chapters 12, 14, 28, and 29, respectively).

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## 5

# The Painful Back

Paul C. Williams

Skeletal Lesions  
Congenital Abnormalities  
Developmental Disturbances  
Destructive Processes  
Arthritis  
Static and Degenerative Changes  
Extraskeletal Lesions  
Neurogenic Lesions  
Parietal Lesions

Visceral Lesions  
Maxillopharyngeal Infection

For reasons of brevity, fractures and dislocation will be omitted and the symptom will be treated with emphasis on the standpoint of the orthopedist. Stress will be given to those condi-

tions which are most frequently encountered. The accompanying classification, though incomplete and imperfect, will be followed for practical reasons.

#### I. Skeletal:

- A. Congenital:
  - 1. Spina bifida
  - 2. Defective development of the pedicles
  - 3. Congenital hemivertebra
  - 4. Sacralization of the fifth lumbar vertebra
  - 5. Lumbarization of the first sacral vertebra
  - 6. Spondylolisthesis
- B. Developmental:
  - 1. Vertebral epiphysitis
  - 2. Scoliosis
- C. Destructive:
  - 1. Infectious
  - 2. Neoplastic
  - 3. Metabolic
- D. Arthritis:
  - 1. Rheumatoid arthritis
  - 2. Rheumatoid spondylitis
- E. Static and degenerative:
  - 1. Degenerative joint disease
  - 2. Intervertebral disk changes
  - 3. Sacroiliac strain

#### II. Extraskeletal:

- A. Neurogenic:
  - 1. Spinal cord tumors
  - 2. Tumors of cauda equina
- B. Parietal:
  - 1. Muscle strain
  - 2. Fibrositis
- C. Visceral
- D. Maxillopharyngeal:
  - 1. Focal infections

The patient who enters complaining of a painful back is deserving of a careful history and an adequate physical examination of the spine. Unfortunately, many cases have undergone pelvic, genitourinary, and oral surgery in an effort to relieve symptoms, without this having been done. A careful history dealing with the onset, persistency, character, and aggravating factors of the pain, accompanied by an examination of the nude back, noting deformities, localizing areas of tenderness, and determining the ranges of motion, is usually convincing as to the source of pain.

## SKELETAL LESIONS

### CONGENITAL ABNORMALITIES

**Spina Bifida.** Spina bifida can be divided into those cases which involve the nerve tissues and those which do not. The latter are spoken of as spina bifida occulta. The former is a neurologic problem which may or may not be improved by surgical treatment. The innervation of the lower extremities is usually affected and a deformity of one or both feet is frequent. A spina bifida occulta, within itself, is not painful but may so alter the mechanics at the lumbosacral articulation that an early degeneration of the intervertebral disk results.

**Defective Development of Pedicles.** Imperfect or asymmetric development of the pedicles is common and so alters the mechanics of the articulations that they not only are more susceptible to strain but also undergo early degenerative joint changes.

**Congenital Hemivertebra.** A congenital hemivertebra causes a lateral curvature which alters the weight-bearing mechanics to the extent that an abnormal stress is placed on the soft tissues, causing early fatigue and associated pain. More severe pain does not occur until secondary degenerative changes have taken place. Such changes consist of hypertrophic lipping of the vertebral margins, principally on the concave side of the curve, and degenerative joint changes of the facet articulations.

**Sacralization of Fifth Lumbar Vertebra; Lumbarization of First Sacral Vertebra.** It is improbable that sacralization of the fifth lumbar vertebra or lumbarization of the first sacral vertebra is, within itself, painful except when an unsatisfactory mobile pseudoarthrosis exists between the malformed transverse process of the fifth lumbar and the lateral mass of the first sacral segment or the ilium. They are potentially painful lesions in that the intervertebral disk immediately above the anomalous segment usually undergoes an early collapse as a result of the abnormal stress to which it is subjected. They also frequently cause early degenerative joint disease, especially in those cases where the first sacral segment is mobile, since its inferior articular facets are usually malformed and, therefore, imperfect in action.

**Spondylolisthesis.** Spondylolisthesis is the most important painful anomaly of the spine. It

is characterized by a bilateral break in the bony continuity of the laminas at their site of union with the superior pedicles of the vertebral body, and a forward displacement of the latter. The term spondylolysis or prespondylolisthesis is applied to those cases which have the break without displacement of the vertebral body. The fifth lumbar segment is most frequently involved, but the condition is also seen in the fourth and occasionally in the third. On rare occasions it may be seen in the cervical spine.

Most of these lesions undoubtedly represent a failure of fusion, but with the improvement in our diagnostic means it has become apparent that a fairly large percentage are traumatic in origin. In the presence of other anomalies of the neural arch, the break in the bony continuity is interpreted as representing a failure of fusion, but with normal development and with bony edges which appear sharp in character the diagnosis of a fracture is favored. This is especially true if pain made its appearance as a result of severe trauma.

Occasionally a pseudospondylolisthesis is seen. This usually is either of two types. One shows an abnormally long isthmus between the neural arch and the centrum without a break in the bony continuity, but with forward displacement of the vertebral body. The other shows parallel anteroposterior facet articulations which permit forward displacement of the entire vertebral segment.

The history related is not constant, since symptoms vary with the degree of displacement and associated intervertebral disk changes. There may or may not be a history of a significant injury. If so, symptoms are usually more severe. The early symptoms are a recurrent dull, aching pain confined to the midline low in the back, aggravated by physical exertion. These patients usually prefer a supine sleeping position on a firm bed, but are unaware of any particular motion of the spine which aggravates more than another.

Most cases do not present themselves until symptoms are more severe. They complain of constant dull, aching pain, with periods of increased severity which are described as "attacks" and are initiated by strain. The pain in the lower part of the back during an attack is severe and frequently accompanied by pain in the lower abdomen, groin, and, occasionally, in

the anterior aspect of the thigh. Appendectomies and pelvic operations are not infrequently performed in an effort to relieve such symptoms. In some cases, symptoms are still more widespread because of a collapsed intervertebral disk. These symptoms will be discussed under this classification.

There is also a variation in the clinical findings. Early cases may present only localized tenderness to pressure over the spinous process of the involved segment. Later, after displacement, there is a prominence of the sacrum, a short lumbar trunk, and a palpable offset between the spinous processes. Major tenderness is localized at the latter site. Motions of the lower spine may be full in range and painless unless the patient is experiencing an acute attack. If so, all motions are limited and painful. The lumbar muscles are in spasm. The straight leg-raising test is usually painless but the Patrick test (Fabre) frequently causes pain in the groin. The knee reflex action may be diminished. Changes characteristic of a collapsed intervertebral disk may sometimes be found.

After displacement has taken place, a diagnosis usually can be made from the history and physical findings alone. However, the character of the lesion and associated disk changes can be determined only by x-ray studies.

The conservative treatment consists of immobilization of the part. If the patient is experiencing an acute attack, this can be accomplished best on a posterior Bradford frame, and relief can be expected in 8 to 10 days. Heat and light massage are valuable adjuncts. Medication for the relief of pain should be administered as indicated. If symptoms of a collapsed lumbosacral disk accompany the clinical picture, the fixation should be carried out in flexion, preferably with the patient on his back in a hospital bed made rigid by boards under the mattress and positioned in flexion as indicated in figure 17. Subacute and chronic cases should be fitted with a brace which extends from the sacrum to the subscapular region. They should be instructed to sleep on a firm bed and avoid heavy lifting or strenuous physical exertion. Quiescent cases are permitted to wear the brace only when taking part in activity which may subject them to a strain of the part.

All cases treated conservatively should report annually for an x-ray examination in order to

determine whether or not there has been further displacement of the involved vertebral body.

Surgical treatment should be done in most cases unless contraindicated by disease or senility, since conservative measures usually restrict the patient to a life of semi-invalidism. A fusion usually affords a satisfactory and lasting relief of symptoms.

### DEVELOPMENTAL DISTURBANCES

**Vertebral Epiphysitis.** Vertebral epiphysitis is probably an aseptic affection of the vertebral epiphyses which makes its appearance during adolescence and involves several contiguous vertebrae, usually in the dorsal region but not infrequently in the upper lumbar. Its cause is unknown, but it is probably due to an epiphyseal nutritional disturbance in which congenital hormone deficiencies and trauma play important roles. It runs a self-limited course over a period of approximately two years and, untreated, results in an anterior wedging of the involved vertebral segments with a resultant kyphosis.

Usually the history reveals a gradual rounding of the shoulders and an inability to stand or sit erect. The parent frequently ascribes this to laziness. The patient complains of a dull, aching pain localized over the involved area and aggravated by physical exertion and fatigue.

The examination reveals an exaggerated dorsal or, occasionally, lumbodorsal kyphosis which is most apparent when the patient bends forward. Jarring with the ulnar aspect of the fist causes moderate pain. The findings are insignificant as compared to those of a destructive lesion such as tuberculosis.

A lateral x-ray study affords more information than does the anteroposterior study. They may reveal the following: anterior wedging of the vertebral bodies, an irregularity of the inferior and superior vertebral surfaces, fragmentation of the epiphyses, narrowing of the intervertebral spaces, and an osteoporosis of the vertebral bodies.

The best results are obtained by removing the weight-bearing factor from the involved epiphyses for a period of four to six months. This is best accomplished by recumbency on a posterior Bradford frame, and should be followed by the use of a Taylor back brace.

Mild cases can be treated while ambulatory by the use of such a brace and altered activity. Sup-

ports should be maintained until x-rays reveal a satisfactory healing of the involved epiphyses. Glandular therapy should be administered as indicated from studies of the specific case.

If the wedging of the vertebrae persists after the growth period, the weight-bearing mechanics are so altered that an early degenerative arthritic change results and causes disability in later life.

**Scoliosis.** A scoliosis is a lateral deviation of the spinal column from the midline. All cases are accompanied by a certain degree of rotation. There are many known causes, but the most common case encountered is the idiopathic. Many theories have been advanced as to its cause; however, none is satisfactory. It is probable that with our increasing knowledge of the intervertebral disk a satisfactory explanation of its etiology will be forthcoming.

The history related varies with the cause. Idiopathic scoliosis predominates in the adolescent female, and frequently the only history related is that of a low shoulder or prominent hip. When the patient complains of discomfort, it is that of early fatigue and aching pain caused by prolonged weight bearing and physical exertion. Radiating pain into the extremities or around the trunk as well as catches in the back following strain are common in later life.

The physical findings likewise vary with the cause. The scoliosis may be an uncompensated single curve or a double compensated curve. Traction on the cervical spine will reveal whether or not the deformity is freely collapsible, as seen in paralytic cases, or fixed, as seen in congenital cases and, to a lesser extent, in idiopathic cases. Both motor and sensory changes may be found in those presenting nerve root symptoms. Such findings are more frequent on the concave side of the curve. Changes characteristic of cardiac and pulmonary embarrassment may be presented. After the third decade of life there may be the findings of a degenerative arthritis of the spine.

The orthopedic treatment consists of exercises, manipulations, corrective jackets, braces, and surgery directed at preventing or correcting contractions and spinal fusions.

### DESTRUCTIVE PROCESSES

**Infectious; Neoplastic.** Destructive lesions are far too numerous to discuss individually in the space allotted. However, there are a few salient

findings common to both infectious and neoplastic lesions which should aid in making the diagnosis. They will, therefore, be dealt with as a unit.

Before making a hasty diagnosis of psycho-neurosis in the patient who complains severely of pain in the back, be sure you are not dealing with a destructive lesion in the form of a neoplasm or infection.

The pain is usually constant and severe. It is aggravated by all motions of the spine and is worse at night. In acute pyogenic infectious cases, the onset is sudden and initiated by chills and fever. A preceding history of an upper respiratory infection or a series of boils is important. In tuberculosis, a history of "night cries" and tuberculous contacts should be suggestive. When a history of the removal of a neoplasm, especially of the prostate, breast, or gastrointestinal tract, is related, metastasis should be considered. The most important historical data to be obtained in those patients with a destructive lesion is that of pain accompanying a slight jar caused by vertical compression or direct violence.

The most important physical finding which should lead one to suspect a destructive lesion is the apparent excruciating pain experienced from jarring the spinous processes with the ulnar aspect of the fist. The effect of jarring also can be determined by having the patient rise to his tiptoes and drop to his heels. As a rule, all motions of the spine are painful and limited. The muscles are in spasm. Many destructive lesions can be suspected correctly before they are apparent in

x-ray studies by close observance of the effects of jarring.

Table 2, when read from above down, lists the most common neoplastic and infectious lesions of the spine in their approximate frequency of occurrence.

**Metabolic.** The most common metabolic cause of the painful back is an osteoporosis of either the postmenopausal or the senile variety. It is frequently difficult to differentiate one from the other in a given case. Both a lack of steroids and senile atrophy are undoubtedly responsible for the picture presented in many cases.

The history is usually that of a gradual rounding of the shoulders and an inability to stand up straight. Pain throughout the entire spine, but especially within the dorsal region and frequently radiating around the chest wall, is a common complaint. Symptoms are aggravated by physical exertion, especially stair climbing. Many do not present themselves until symptoms become acute. Such cases frequently complain of a sudden severe onset of pain localized to a definite region following some trivial injury.

The findings vary with the duration. Early, generalized tenderness throughout the entire spine is about the only clinical finding. Later there is an exaggeration of the dorsal kyphosis, and spinal as well as costal motions are limited in their ranges. When a patient presents acute symptoms on primary examination, they are usually due to a vertebral compression fracture. There is usually a prominence of the spinous process of the involved segment with marked

Table 2  
COMMON NEOPLASTIC AND INFECTIOUS LESIONS LISTED BY FREQUENCY OF OCCURRENCE

		<i>Neoplasms</i>			<i>Infections</i>	
		<i>Malignant</i>				
<i>Benign</i>	<i>Primary</i>	<i>Generalized</i>	<i>Metastatic</i>			
Giant cell Osteochondroma Bone cysts Chondroma Hemangioma	Osteogenic sarcoma 1. Chondrosarcoma 2. Osteolytic sarcoma 3. Sclerosing sarcoma Chondroma	Multiple myeloma Hodgkins granuloma Lymphosarcoma	Breast Esophagus Thyroid Uterus Bronchus Stomach Prostate	Tuberculosis Osteomyelitis (pyogenic) Brucellosis (undulant fever) Blastomycosis Actinomycosis Oidiomycosis (coccidioidosis) Syphilis Typhoid		

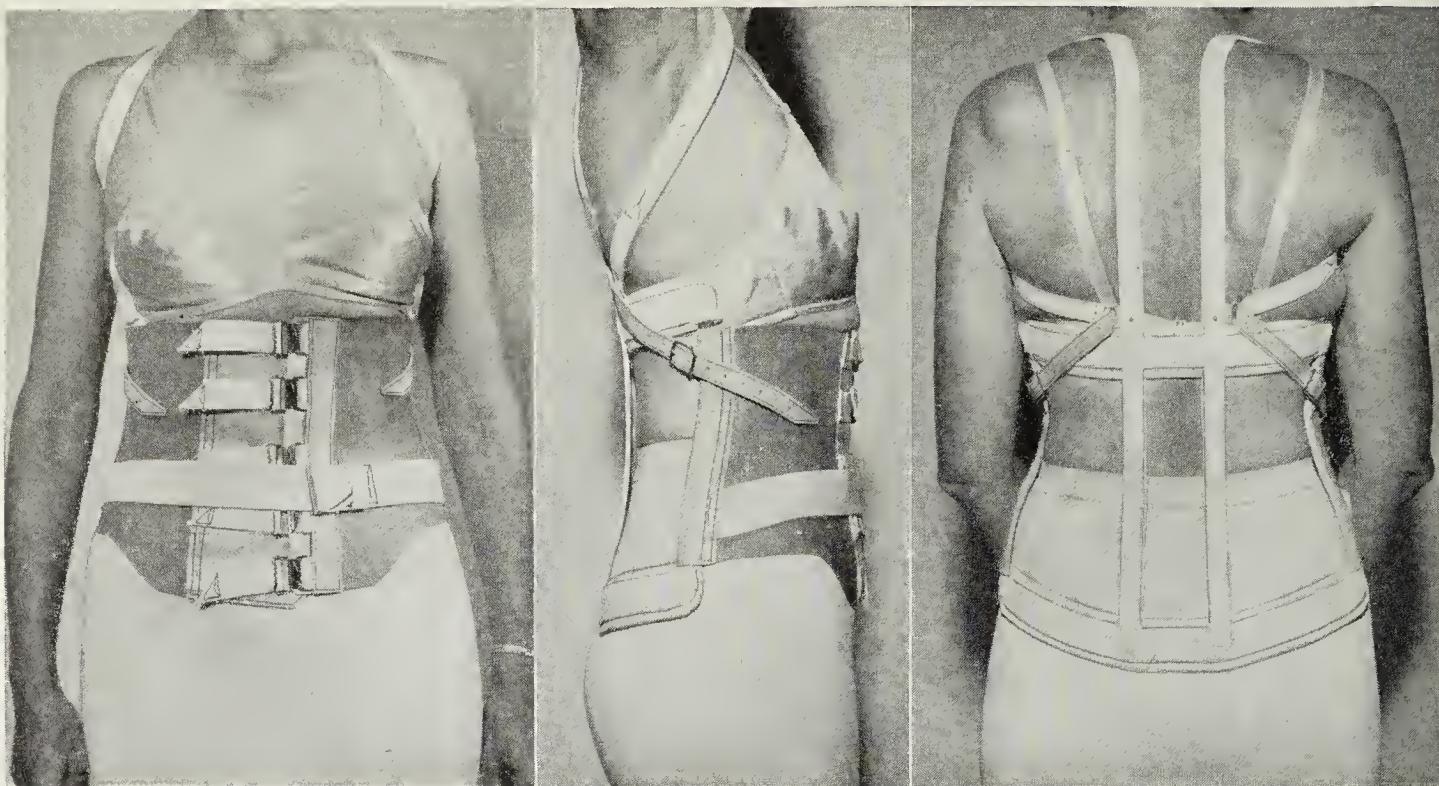


FIG. 9. Modified Taylor brace, used principally in cases of osteoporosis of the spine.

tenderness to pressure or percussion at this site. The adjacent muscles are in spasm.

X-rays early in the disease show only a decalcification of the vertebral bodies. Later the nuclear (nucleus pulposus) indentations become exaggerated, giving the typical codfish vertebra appearance, and finally resulting in anterior wedging and complete compression of the vertebral bodies.

Treatment consists of a spinal support. A light-weight modified Taylor brace is usually more effective and comfortable than corsets (fig. 9). Such a brace should be considered as part of the permanent wearing apparel. The patient is advised to be active and if possible to walk at least one mile a day in order to avoid further disuse osteoporosis. Those who have recently suffered a compression fracture frequently must be confined to a rigid bed until acute symptoms have subsided. No further attempt at reduction should be made. The rest period should be not over three weeks, and less if possible. The patient then is fitted with the brace mentioned, and activity is encouraged. Under such circumstances considerable discomfort usually persists for about 10 weeks, but by following such a program further disuse atrophy is reduced to a minimum.

A regulation of the deficiency factor by means of steroids, vitamins, and diet is of prime importance and is discussed in Chapter 66.

## ARTHRITIS

Many contend that rheumatoid spondylitis is but a different manifestation of rheumatoid arthritis, but because of differences in the clinical and laboratory findings they must be considered as independent diseases until their etiologic factors are better known.

A commonly accepted theory at present is that both are of an infectious origin and are caused by bacterial proteins which act as an antigen, sensitizing tissues so that additional bacteria or proteins produce an allergic reaction.

The differences in the clinical course and laboratory findings of the two diseases may be due to endocrine differences within the individuals, since the rheumatoid arthritic patient presents symptoms suggesting a glandular deficiency more commonly than does the patient with rheumatoid spondylitis. This is especially true in skeletal growth and can be demonstrated by comparing the length of the long bones with that of the trunk.

The recent announcement of the remarkable effects of cortisone (an adrenal cortical hormone) in rheumatoid arthritis by Hench, Kendall, Slocumb, and Polley points strongly to a true substitution therapy for this disease (Chapter 39).

**Rheumatoid Arthritis.** Rheumatoid arthritis of the spine may be associated with a generalized rheumatoid arthritis or it may affect the spine

alone. The latter condition is seen most commonly during the fourth decade of life. Its frequency of occurrence is about the same in both sexes. A history of chronic sinusitis or other allergic symptoms is common.

The history is usually that of a gradual onset of generalized stiffness and soreness of the back aggravated by seasonal and barometric changes. The pain is worse in the morning and is relieved partially by activity. Radiation of pain is uncommon. Acute localized symptoms follow strain or injury.

The spine has a tendency to move as a unit. Chest expansion is limited. Usually there is an exaggeration of the normal dorsal kyphosis. Movements of the spine are only moderately painful. There is tenderness to both jarring and pressure throughout the dorsal and lumbar spines. Following strain or injury, major tenderness may be localized to a definite area.

X-rays rarely show changes within the vertebral body, intervertebral disk, or longitudinal ligaments, but detailed studies of the facet articulations reveal changes characteristic of an atrophic arthritis. The sacroiliac joints are always involved in the process.

Local treatment consists of postural exercises, a rigid sleeping position, and physiotherapy in the form of heat and light massage. A spinal support is indicated if exercises fail to prevent a progressive deformity. General treatment consists of combating infection and avoiding mental and physical fatigue. Medication should be directed at relieving pain as well as correcting anemic and metabolic disturbances. In those presenting evidence of chronic upper respiratory infection, additional treatment should be directed at a desensitization to allergic factors or the changing of the bacterial flora by altering the climatic environment.

**Rheumatoid Spondylitis.** Rheumatoid spondylitis is a fairly common cause of the painful back. The relative sex incidence strongly favors the male. It usually makes its appearance in the third decade of life and runs a more virulent course than does spinal rheumatoid arthritis. Its cause is unknown but the same theories apply as in rheumatoid arthritis.

The patient complains of a gradual onset of pain and stiffness in the lower back. The severity of pain varies with physical exertion. "Catches" is a term frequently applied to acute episodes

following strain. Stiffness and soreness are more marked after a period of inactivity and are aggravated by barometric changes. Heat usually affords temporary relief.

The findings vary with the duration, severity, and location of the disease. It usually starts in the sacroiliac joints and progresses upward, although it is not uncommon to see in x-ray studies vertebral segments which apparently have been skipped in the upward progress of the disease. The hip joints are frequently involved and present various degrees of fixation. As the disease progresses the spine becomes fixed, the chest flattens, and the abdomen protrudes. Chest expansion is lost and the head protrudes forward in a fixed position. Tenderness to percussion or pressure over the involved segments is the rule with intermittent episodes of localized acute tenderness accompanied by spasm of the adjacent muscles, especially following injury or strain.

Untreated cases, when seen after the fifth decade of life, usually present a firm painless ankylosis of the entire spine and frequently of the hips.

Rarely, ankylosing spondylitis starts in the upper spine, affecting first the cervical vertebrae and progressing downward. This type usually occurs at a later period in life and frequently involves the shoulder joints.

The characteristic x-ray change which differentiates this disease from rheumatoid arthritis is the ossification of the paraspinal ligaments. In addition, the x-rays reveal a demineralization of the vertebral bodies and an atrophic arthritic involvement of the apophyseal and costovertebral articulations. The intervertebral disks are usually unaffected. Synovial involvement and symptoms exist before the usual x-ray picture is presented.

Early in the disease the sacroiliac joints present a haziness with areas of sclerosis and decalcification. As the disease progresses, fusion of these joints becomes apparent.

Local treatment consists of postural exercises and a firm sleeping position without a pillow. If a flexion deformity of the upper spine has already appeared and the disease is not in a late stage, a period of fixation on a posterior Bradford frame frequently will partially correct the deformity. This should be followed by the use of a Taylor type brace at all times while the patient is ambulatory. Regular heat and light massage are beneficial to the patient's comfort.

X-ray therapy applied to the affected parts is of value. Whether it modifies the course of the disease or merely relieves pain has not been determined. The usually accepted technic is that described by Smyth, Freyberg, and Lampe. The course should be given to all involved areas at intervals of three to six months, and repeated three consecutive times, if necessary.

General measures, as in rheumatoid arthritis, should be directed at improving the general health.

### STATIC AND DEGENERATIVE CHANGES

Static and degenerative lesions of the spine are the most common cause of the painful back and will, therefore, be dealt with in more detail.

Man is the only animal who has successfully acquired the ability to balance a bulky superstructure on a small base of support. His success has been due primarily to evolutionary changes which have increased the pelvic perimeter, especially in its posterior aspect, thus affording an origin for the extensor muscles posterior to both the lumbosacral and the hip joints. This has made it possible for him to hyperextend the hips and the lumbosacral spine. His base of support actually amounts to a circular base approximately 5 feet in diameter, any phase of which may be utilized instantly to rebalance a disturbance within the center of gravity of the superstructure.

The hip joint has accommodated itself well to the evolved position. This has not been true with the spine, since its functional alteration has been more radical. The vertebral bodies and the intervertebral disks have become weight-bearing structures and the spine has become a series of lordotic and kyphotic curves. A lordotic curve is of clinical importance because the vertebral articulations and the neural structures lie posterior to the vertebral bodies and are, therefore, subject to a compressive force.

When man first acquired the upright attitude is still not definitely known. That it is an intrinsic rather than an acquired characteristic remains to be proved.

Good posture is that state of muscular balance which affords minimal trauma to the weight-bearing structures, irrespective of attitude assumed. Such postures are rare in modern urban civilization, as a result of occupations, habits of

dress, and fallacious teachings as regards attitudes of standing, walking, sitting, sleeping, etc. The old military posture, as exemplified in the "strut" attitude, with chest elevated and back arched, undoubtedly accounts for many of these teachings.

**Degenerative Joint Disease (Degenerative or Hypertrophic Arthritis).** A traumatic irritative factor is the generally accepted cause of degenerative arthritis. It is found to involve principally the weight-bearing articulations. Any factor which so alters the mechanics of a joint that it causes abnormal stress and strain will result in degenerative changes within the articulation. The degree of change varies with the constitutional type and is undoubtedly influenced by nontraumatic inflammatory processes.

Hypertrophic arthritis of the spine should be considered as physiologic in character. It can be demonstrated, at least in a mild form, on the x-rays of most individuals in middle and late life. It appears earlier in those who have a gross disturbance in the weight-bearing mechanics of their spine and also in those who have been subjected to injury or to strenuous physical occupation. An important immediate cause of hypertrophic arthritis of the spine is a traumatic or degenerative change within the intervertebral disk which deprives it of its resilient intervertebral support.

The symptoms of this disease are characterized by exacerbations and remissions. In many who have the disease, symptoms are quiescent and may remain so for an indefinite period of time. The clinical picture is, therefore, inconstant. When symptoms are mild, common complaints are fatigue, stiffness, and aching pain most noticeable after arising or after sitting for some time. The symptoms are usually relieved by activity. Radiating pain following the distribution of one or more of the spinal nerves is common. Barometric and temperature changes as well as constipation and focal infections usually aggravate symptoms. Occipital headaches are common and frequently severe in those with a marked involvement of the cervical spine.

An active degenerative arthritic involvement of the sacrococcygeal or intercoccygeal articulations commonly causes a constant pain which is aggravated by the sitting position. Secondary symptoms of psychoneuroses are not infrequent in these cases.

Those experiencing an acute exacerbation commonly relate a history of a sudden onset of severe pain as a result of strain caused by lifting, twisting, etc. The pain is frequently so severe that the patient resists the least movement. The situation may be considered an emergency by the patient and the family.

The usual findings of degenerative arthritis are painful restricted motions and tenderness to deep pressure. When symptoms are acute, these findings are more marked and accompanied by protective spasm of the adjacent muscles.

In treating degenerative arthritis of the spine, it is important that the patient not be told that he has arthritis unless such a statement is followed by an explanation that the changes presented are, to a large extent, physiologic in character and represent the wear and tear of an active physical life or a disturbed weight bearing, as the case may be. Without such an explanation the patient is apt to assume that he will rapidly become an invalid.

In those lacking acute symptoms but experiencing chronic discomfort, any or all of the following may be used to advantage: mobilization, heat, massage, x-ray therapy, medication, and reduction of weight in the case of obese patients. Such reduction of weight may produce marked benefit by decreasing the load on the vertebral column.

Mobilization is most effective when the changes are not severe and when it is the lumbar or cervical spine that is primarily involved. Pain is likely to increase as motion becomes limited. Extension exercises are to be avoided in order to prevent irritation of the nerve roots and injury to the already overstretched capsules and ligaments of the apophyseal articulations. Exercises at both sites should be directed at increasing the range of flexion. Such exercises are described under the treatment of disk changes.

Daily heat and light massage are valuable palliative measures. Counterirritants are useful when the application of heat is impracticable. In degenerative arthritis of the sacrococcygeal articulation, heat can best be applied by hot sitz baths. These should be taken twice daily until symptoms have been relieved. Warm retention enemas are also effective, but the patient should be warned that in using these the rectal mucosa cannot be relied upon for the determination of temperature. An injection of 0.5 per cent pro-

caine in saline solution into and around the joint frequently gives relief. Surgical removal of the coccyx along with the distal half of the fifth sacral segment is usually effective in those cases which do not respond to conservative treatment. However, this should not be done unless a definite diagnosis of a degenerative arthritis with limited painful motion can be made.

Those suffering an acute episode with symptoms localized in the dorsal region should be immobilized. This is best accomplished on a posterior Bradford frame. The knees should be propped up with pillows to avoid extension of the lumbosacral joint. Fixation should be continued for 7 to 10 days. X-ray therapy and heat may be valuable adjuncts, but all unnecessary motion of the involved area should be avoided.

Those with chronic disabling symptoms whose x-rays show extensive degenerative changes should be treated by immobilization rather than mobilization. Such treatment includes a brace and a rigid sleeping position in addition to the therapeutic measures already mentioned. When the involvement is principally within the cervical spine, a cervical traction apparatus attached to the bed in the home and worn at night adds to the patient's comfort.

**Intervertebral Disk Changes.** Acute or chronic traumatic destruction of the intervertebral disk accounts for the majority of painful backs. It occurs most frequently at those two sites where motion is greatest and where the spine is hyperextended—namely, the lumbar and cervical regions.

The term collapsed rather than ruptured will be used in signifying traumatic intervertebral disk changes. The latter term is inclined to give the impression that all disks suddenly burst, forcefully expelling their nuclear content.

The component parts of the intervertebral disk are the annulus fibrosus, nucleus pulposus, and the two cartilaginous plates. In youth, the nucleus pulposus is a soft, semigelatinous substance ovoid in shape and confined by the limiting annulus fibrosus and cartilaginous plates. It, rather than the annulus fibrosus, furnishes the resilient intervertebral support.

Acute traumatic compression may so increase the pressure within the nucleus pulposus that either a herniation of the cartilaginous plate or a rupture of the annulus fibrosus may take place. In either event, the intervertebral space becomes

narrower and a partial subluxation of the joints formed by the facets results.

Chronic traumatic compression results in degenerative changes in the intervertebral disk. There is evidence to support the belief that the degenerative change first takes place in the annulus fibrosus, opening avenues of escape for the nuclear content which in turn undergoes a desiccation and fibrous degeneration with a resultant narrowing of the intervertebral space. Such changes are common in the lower lumbar disks in the third and fourth decades of life. However, Compere and Keys found that "in discs unaffected by pathological processes, the nucleus pulposus retains its semigelatinous consistency even beyond the fifth and sixth decades."

From the time an infant acquires sufficient strength within the spinal muscles to counteract the pull of gravity, these muscles remain in a more or less constant state of contraction throughout life. The opposing abdominal muscles are placed under constant stretch and are rarely forcefully contracted. Any muscle or group of muscles lacking normal opposition produces a deformity of the part. It is a hyperextension deformity of the lumbosacral spine produced by an elevation of the back of the pelvis. Below the pelvic brim, the hip flexors act as does the erector spinae in elevating the back of the pelvis and thus increasing the lumbosacral extension. They are protected from chronic stretch by the strong tensor fasciae. The glutei maximi act as do the abdominals in elevating the front of the pelvis, but they, like the abdominals, become weak in our sedentary urban existence. These muscles are all important in squatting and in climbing, but both of these activities we avoid if possible. Like the abdominals, they are more or less under constant abuse. The tendency, therefore, is toward an increasing lumbosacral extension with a transmission of the weight of the trunk to the posterior aspect of the annulus fibrosus of the lower lumbar, and especially the lumbosacral, intervertebral disks.

As a compensatory mechanism the cervical lordosis and the dorsal kyphosis vary with the degree of lumbosacral lordosis. The situation in the cervical spine is very similar to that of the lumbosacral in that the muscles of flexion are rarely used while the antigravity or muscles of extension are in almost constant use. The former become weak and elongated while the latter be-

come strong and shortened, thus compressing the posterior aspect of the intervertebral disks.

**LUMBOSACRAL SPINE.** More than 80 per cent of those who seek treatment with the complaint of pain in the lower part of the back are found to be suffering from collapse of one of the lower lumbar intervertebral disks, usually the fifth.

A carefully taken history is as important in arriving at a diagnosis as is the physical examination. A history commonly related is that of an acute onset of pain in the lower part of the back, usually caused by a forceful hyperextension injury. Repeated episodes termed as "lumbago" or "catches" follow for a period of months or years, until eventually attacks are accompanied by pain radiating down one of the lower extremities. The most common distribution is down the back and side of the thigh and calf into the lateral aspect of the ankle and foot. Less frequently, the pain radiates into the front of the thigh or down the back of the thigh and calf and into the heel. The distribution of pain is dependent upon the nerve root affected.

The usual history in chronic cases lacks acute episodes. The pain may or may not radiate down the legs. Symptoms are usually continuous, but affected by activity and positions.

The most striking mechanical factor to be learned from the historical data is that extension of the lumbosacral spine increases pain, whereas flexion reduces it. Common related examples are:

Sleeping on the abdomen increases pain, while sleeping on the side with one or both knees drawn up reduces pain.

Sitting in an erect attitude increases pain, but sitting with the knees propped up or with the trunk bent forward reduces pain.

Bending over a wash basin increases pain, but by partially bending the knees and hips, thus flexing the lumbosacral spine, the position can be maintained without appreciable discomfort.

Lifting a load in front of the body at or above the waistline increases pain.

Working with the hands and arms over the head increases pain.

When symptoms are acute, sneezing causes sharp pain unless done with the knees and chest approximated.

Dancing, especially in women, increases pain.

There are numerous other examples which aggravate symptoms, such as prolonged standing,

sitting in a theater, rising from a sitting position, and driving a car, all of which cause an increase in lumbosacral extension.

Excepting during an acute episode, walking is not related as a common cause of aggravation, but when it is cited it suggests a sacral obliquity due either to a short leg or to an asymmetric development of the sacrum.

The examination should be made with the back, hips, and thighs of the patient completely nude. Table 3 lists the usual findings.

The x-ray studies should include a single lateral, a tilted stereo anteroposterior, and single oblique views of the lumbosacral spine. The principal x-ray changes which follow a destruction of the intervertebral disk are: subluxation of the adjacent facet articulations with a constriction of the foramen (fig. 10); posterior displacement of the segment immediately above the involved disk (fig. 11); narrowing of the intervertebral

space (fig. 11); contact of adjacent spinous processes; marginal lipping on adjacent vertebral surfaces caused by abnormal stress resulting from loss of the resilient intervertebral support; lodging of the superior margins of the first sacral facets in the inferior vertebral notches of the fifth lumbar vertebra, thus transforming the superior first sacral facets into weight-bearing structures and causing sclerosis of the latter as well as sclerosis within the inferior vertebral notches and occasionally osteophyte formation at the latter site (fig. 12).

The subluxation of the facet articulations is the most important diagnostic change. The technic employed in making the x-ray exposure is very important in obtaining satisfactory facet studies. Myelograms should be made on those cases which fail to respond to an adequate conservative program. A defect will be apparent at the level of the involved disk in many cases, and

*Table 3*  
USUAL FINDINGS IN COLLAPSE OF LOWER LUMBAR INTERVERTEBRAL DISK

	<i>Acute</i>	<i>Chronic</i>
Inspection.....	Spinal list with flat or kyphotic lumbar spine. Stands favoring affected extremity	Malposture with exaggerated lumbosacral lordosis. A lateral pelvic tilt when in weight-bearing position in about 20 per cent of cases
Palpation.....	Marked tenderness to thumb pressure at lumbosacral articulation and sciatic notch of affected extremity. Spasm of spinal muscles	Moderate tenderness to thumb pressure at lumbosacral articulation and sciatic notch on one or both sides
Motions and manipulations	Ranges of lower spinal motions are severely restricted. Extension and lateral flexion toward affected side frequently cannot be executed; attempts cause severe pain. Straight leg-raising test reveals hamstring spasm and causes pain along course of sciatic nerve and at lumbosacral level. Same test on unaffected side reveals less hamstring spasm with pain at lumbosacral level on affected side. Tensor fasciae may or may not be taut	Ranges of lower spinal motions are moderately limited, especially anterior flexion. Hyperextension is usually painful. Straight leg-raising test frequently reveals hamstring limitation without pain of sciatic nerve. Ranges of hip joint motions are unaffected. Tensor fasciae may or may not be taut
Measurements.....	A short leg is found in about 15 per cent of cases. Atrophy of affected thigh and calf is common	A short leg is found in about 15 per cent of cases. Circumference of thighs and calves are usually same
Neurologic findings....	Decreased or lost sensation to pinprick over lateral aspect of distal thigh, calf, ankle, and foot on affected side is frequently found. Less frequently same changes are found over anterior aspect of thigh. Achilles tendon reflex action is usually decreased or absent. Partial paresis of extensor hallucis longus, peroneals, long extensors, and (less common) the tibials, long flexors, and gastrocnemius, is not infrequent	Increased sensation to pinprick on lateral aspect of calf and ankle on one or both sides is common. Achilles tendon reflex action may be increased, decreased, or unaffected. Muscle function of feet and legs is unaffected. There are no pathologic reflexes



FIG. 10. Oblique study of lumbosacral articulation, showing a subluxation of the lumbosacral facets (retouched).

is usually indicative of a herniated nucleus pulposus (fig. 13).

Treatment of the lesion under consideration must be along mechanical lines, as the lesion itself is mechanical in character. An understanding of the pathologic changes is important in establishing correct mechanical principles of treatment. Figure 14 shows the anatomic relationship and some of the changes which accompany a collapse of the lumbosacral intervertebral disk. The superior margin of the first sacral facet is lodged in the inferior vertebral notch. The anterior superior aspect of the facet is contacting the funicular portion of the fifth lumbar nerve. The prolapse of the annulus fibrosus and the subluxation of the joint are shown. It is apparent from a study of the specimen that contraction of the erector spinae at a time when the lumbosacral joint is in an extended position will tend to elevate the sacrum, which in turn further subluxates the facet articulations and forces the anterior superior aspect of the first sacral facets into firm contact with the fifth lumbar nerves within the foramen. It is also apparent that such action further stretches the joint capsules



FIG. 11. Lateral study of the lumbosacral articulation, showing posterior displacement of the fifth lumbar vertebra, narrowing of the lumbosacral intervertebral space, constriction of the lumbosacral foramen, and degenerative changes involving the superior aspect of the first sacral facets.

which have already lost their factor of safety motion. Most acute attacks occur under such conditions; for example, when lifting a load above the waistline or when raising a resistant window.

The erector spinae and the hip flexors are the most important extensors of the lumbosacral spine. The anterior abdominals and glutei maximi are the most important flexors of the lumbosacral spine. Treatment should be directed at reducing the lumbosacral extension, thereby relieving the posterior pressure at this site. It is, therefore, necessary to develop actively the flexors of the lumbosacral spine and to stretch passively the extensors in order to obtain and maintain a satisfactory postural balance and thus reduce lumbosacral extension.

The symptoms resulting from a collapsed lumbosacral intervertebral disk may be acute, chronic, or quiescent. The treatment must be instituted accordingly. The majority of persons beyond the fourth decade of life have a partial

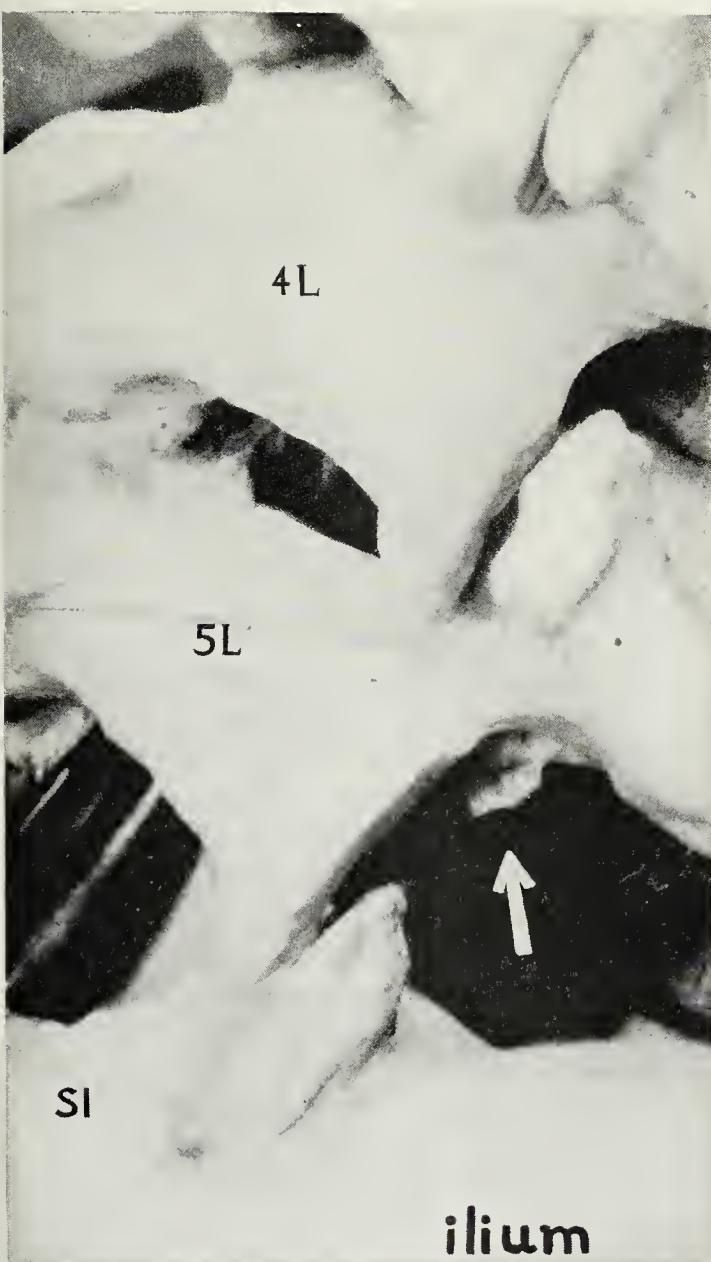


FIG. 12. Skeletal material showing osteophyte formation within the inferior vertebral notch of the fifth lumbar vertebra, and eburnation of the first sacral facet resulting from the latter being transformed into a weight-bearing structure. (Courtesy, Williams: *Radiology*, 30:361, 1938.)

collapse of the lumbosacral intervertebral disk and, thus, a potentially painful lesion.

Those suffering from chronic symptoms constitute the majority of "low back" patients who report for treatment. In this group, the aggravation of symptoms by bending over a wash basin, rising from a sitting position, prolonged standing, and sleeping on the abdomen is a common complaint. Treatment consists of the institution of a postural program. If the patient presents a sacral obliquity, it should be compensated for by a lift on the heel of the shoe unless pain radiates down the short extremity. If such is the case, a compensatory lift will usually increase nerve symp-



FIG. 13. Myelographic defect on the left side at the level of the fourth lumbar intervertebral disk, indicative of a herniated nucleus pulposus.

toms. If pain radiates down the long extremity, the compensatory lift frequently affords relief. After correcting lumbosacral weight bearing in the lateral plane, efforts are then directed at its correction in the anteroposterior plane—that is, a reduction of the lumbosacral angle.

An exercise program directed at actively developing the flexor muscles of the lumbosacral spine and passively stretching the extensor muscles is instituted. Exercise 1, figure 15, is directed at actively developing the anterior abdominal muscles. The patient should not anchor the feet, because in so doing the hip flexors are thrown into active contraction. Whether a patient can rise to a full sitting position or only part way depends not on muscular strength but rather on the relative weight of the trunk and the lower extremities, the buttocks acting as a fulcrum.

Exercise 2, figure 15, is directed at actively developing the glutei maximi. The pelvis is rotated forward by an active contraction of these muscles. The hands are placed on the abdomen just above the umbilicus and should hold the upper abdomen down so that flexion takes place only at the lumbosacral spine.

Exercise 3, figure 15, is directed at passively stretching the erector spinae and at the same time restoring flexion to the lumbosacral spine. The grip on the knees should not be released during the course of the exercise. The thighs should

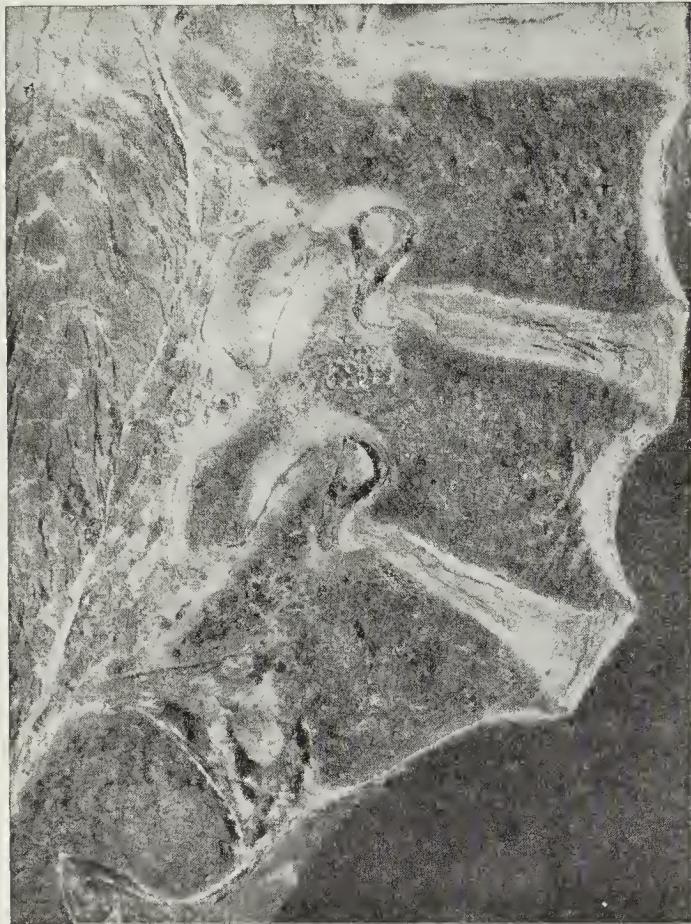


FIG. 14. Anatomic specimen showing collapsed lumbo-sacral intervertebral disk, subluxation of the lumbosacral facets, constriction of the foramen, and contact of the fifth lumbar nerve with the first sacral facet. (Courtesy, Dr. Yglesias and courtesy, Williams: *J. Bone & Joint Surg.*, 19:343, 1937.)

be spread apart in order to avoid contact with the abdomen or chest. The knees are then pulled back and forth in an effort to bring them into the axillas. One should avoid trying to pull the knees above the shoulders since this results in flexion of the upper dorsal and cervical rather than the lumbosacral spine.

Exercise 4, figure 15, is directed at restoring lumbosacral flexion and stretching the erector spinae. Still more important is its action in stretching short hamstring muscles in those cases who have experienced protective hamstring spasm over a long period of time. This exercise is not indicated in acute cases with pain radiating into an extremity.

Exercise 5, figure 15, is intended for stretching the fascia lata, which is not necessary in all cases.

Its advisability is determined by physical examination. When the fasciae latae are even moderately taut its use is important and will be found to be quite effective when practiced over a period of time. The foot on the flexed extremity should be placed and remain flat on the floor while the foot on the extended extremity should be dorsiflexed so that weight is borne on the ball of the foot rather than on the tips of the toes. By flexing the forward knee, the pelvis is moved up and down, the downward motion being effective in stretching the taut structures.

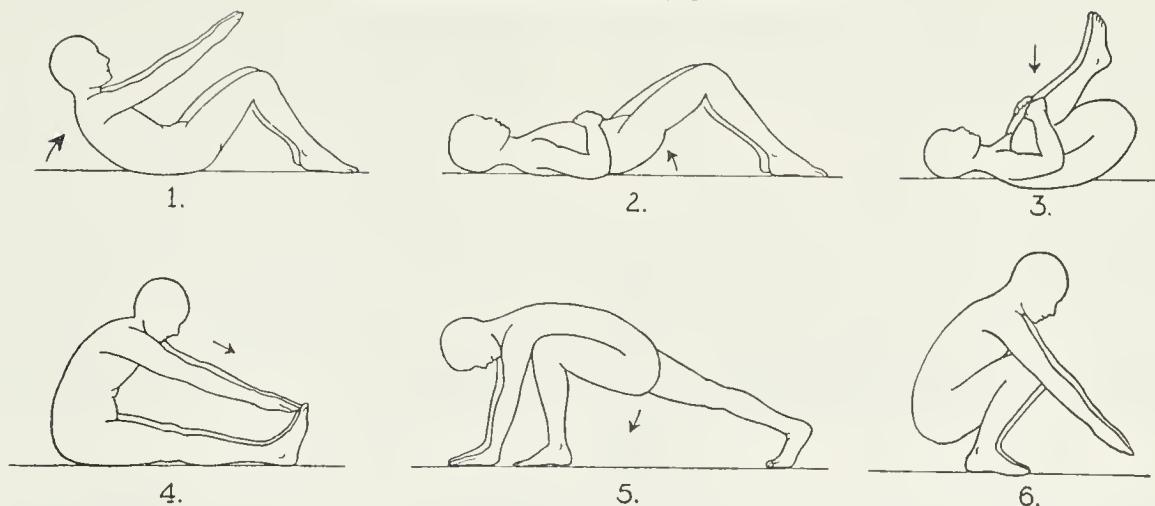
Exercise 6, figure 15, the "flat-footed squat" which has been emphasized by Regen, is most valuable and is directed at actively developing the abdominal and gluteal muscles. The feet are placed parallel and about 15 inches apart. The patient then squats with the back rounded until the buttocks are about eight inches from the floor. The total roundness of the back is important. The heels should not be raised from the floor. Many find it impossible to do this exercise as outlined, but through persistent effort they can usually accomplish it. Such persons should use a weight of 6 to 8 pounds held out in front of the trunk to act as a counterbalance. Still others are so disabled that they are instructed to start by attempting to arise from a sitting position on a stool about 8 inches high by using a weight as a counterbalance if necessary.

The exercises as outlined should not be altered unless considerable thought has been given to the mechanical action involved. As an example, exercise 4 could be taken in a standing position, but, if so done, it would result in an active development of the erector spinae muscles which are already overdeveloped and to a large extent responsible for symptoms.

The exercises are essential in obtaining proper muscular balance and restoring flexion to the lumbosacral spine, but good posture is acquired only through conscious effort. The patient is taught to live 24 hours a day with extension of the lumbosacral spine reduced to a minimum. This requires instructions in standing, walking, bending, sitting, and reclining.

Standing and walking should be done in a position of "forward attack." The chest should be the part farthest forward of the trunk. The front of the pelvis should be lifted so that it approximates the xiphoid cartilage, thus producing a crease across the upper abdomen. The feet should

## POSTURAL INSTRUCTIONS



Exercises should be taken on a padded floor.

Exercise 4 should be omitted unless otherwise instructed.

Start exercises by doing each one \_\_\_\_\_ times morning and evening, increasing the series one a day until you are doing each one \_\_\_\_\_ times morning and evening.

Exercises are essential in obtaining a proper muscular balance but a correct posture is acquired only through conscious effort.

**Remember—**

1. When standing or walking, toe straight ahead and take most of your weight on heels.
2. Try to form a crease across the upper abdomen by holding the chest up and forward and elevating the front of the pelvis.
3. Avoid high heels as much as possible.
4. Sit with the buttocks "tucked under" so that the hollow in the low back is eradicated.
5. When possible, elevate the knees higher than the hips while sitting. This is especially important when driving (driver's seat forward) or riding as a passenger in an automobile.
6. Sleep on your back with knees propped up or on your side with one or both knees drawn up. Bed should be firm.
7. Do not lift loads in front of you above the waist line.
8. Never bend backwards.
9. Do not bend forward with knees straight. Always "squat."
10. Avoid standing as much as possible.

**Learn to Live 24 Hours a Day Without a Hollow in the Lower Part of Your Back**

FIG. 15. Postural instruction sheet, furnished to each patient following a thorough instructional course.

be pointed straight ahead and most of the body weight should be borne on the heels. To carry the weight on the balls of the feet causes a forward shift in the base of support which is compensated by a forward thrust of the pelvis and a backward thrust of the upper trunk, with a resultant increase in lumbosacral extension. Excessive use of high heels should be avoided since any elevation of the heel shifts the base of support forward and thus increases lumbosacral extension.

When in the erect attitude, patients are taught to get up and down by first flexing the lumbosacral spine and then "squatting." The latter should consist of acute flexion of both the hips and knees. A load should not be lifted with the knees in extension as shown in figure 16. Instead, it should be lifted with the legs and the lumbosacral spine in flexion. A load should not be carried in front of the body at the level of or above the waistline except with the lumbosacral spine

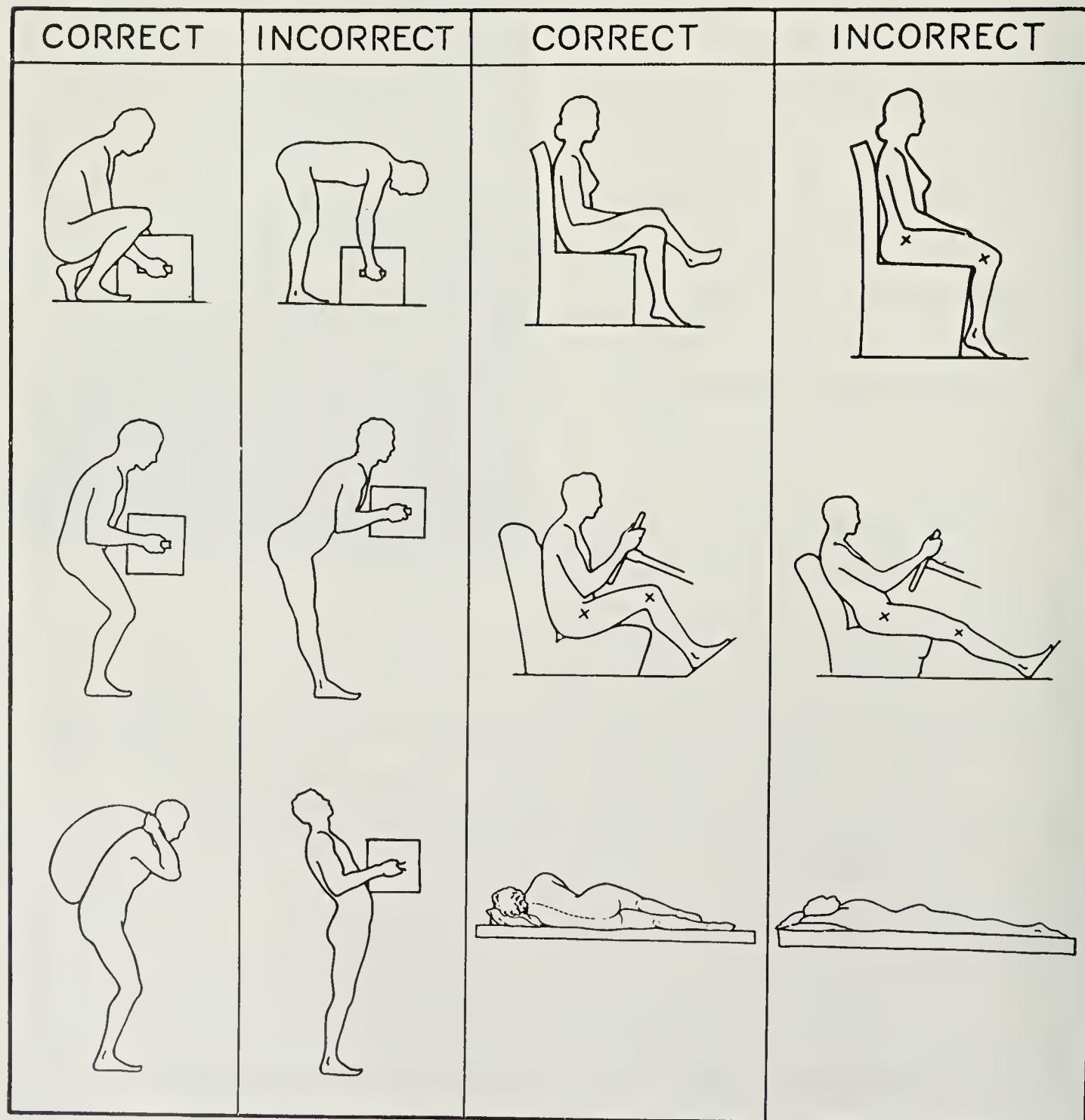


FIG. 16. Reverse side of postural instruction sheet, showing correct and incorrect methods of lifting, sitting, and sleeping.

rounded and the hips and knees partially flexed as in figure 16.

Sitting should be done with the buttocks "tucked under," thus flexing the lumbosacral spine. It is advisable to elevate the knee joints above the hips in order to flex further the lumbar-sacral spine. Most chairs are too high for the average woman, causing her to sit with the knees at a level lower than the hips, thus extending the lumbar-sacral spine as shown in figure 16. It is customary and commendable for women to overcome this position by crossing the knees (fig. 16), but a stool is usually necessary if comfort is to be maintained in prolonged sitting on such a chair.

A correct driving position is of special importance to those whose occupation demands this mode of travel. The driver's seat should be pushed forward, thereby raising the knees to a higher level than the hips and so tending to reduce lumbar-sacral extension as illustrated in figure 16. The frequent complaint of inability to sit through a show is due largely to the inclination of a theater floor, which requires that the knees come to a rest at a plane lower than the hips, thus increasing lumbar-sacral extension.

Sleeping on the abdomen should be avoided and the patient taught to sleep on the side with one or both knees drawn high enough to flex the lumbar-sacral spine as shown in figure 16. Sleeping on the back with the knees elevated is recommended as the most effective sleeping position.

Should the patient turn on his side during sleep because of the elevation of the bed, he will unconsciously draw up one or both knees. The most efficient flexed position of sleeping is obtained by the use of a hospital bed as shown in figure 17.

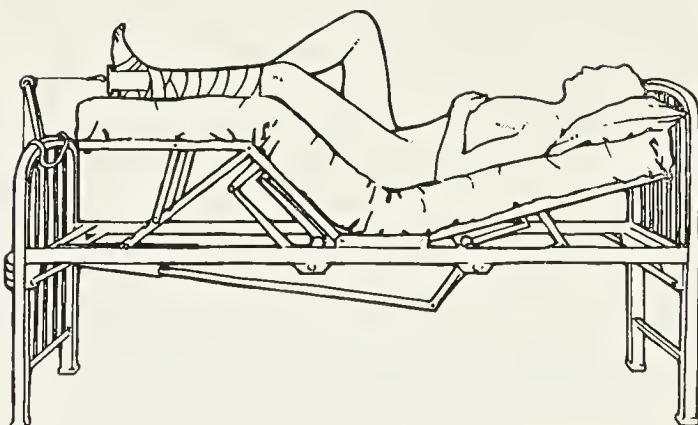


FIG. 17. Hospital bed showing position of flexion. The illustration also shows the method of applying traction in acute cases with sciatic nerve radiation.

Its permanent use is recommended in many chronic cases, especially in elderly persons and pregnant women, where mechanical means of correction have to be employed more frequently.

Mechanical support is reserved for those cases who lack ability to obtain or maintain satisfactory postural position. When a mechanical support is indicated, a lumbar-sacral flexion brace of the three-point pressure principle, designed by the writer, is usually employed. Various views of such a brace are shown in figure 18.

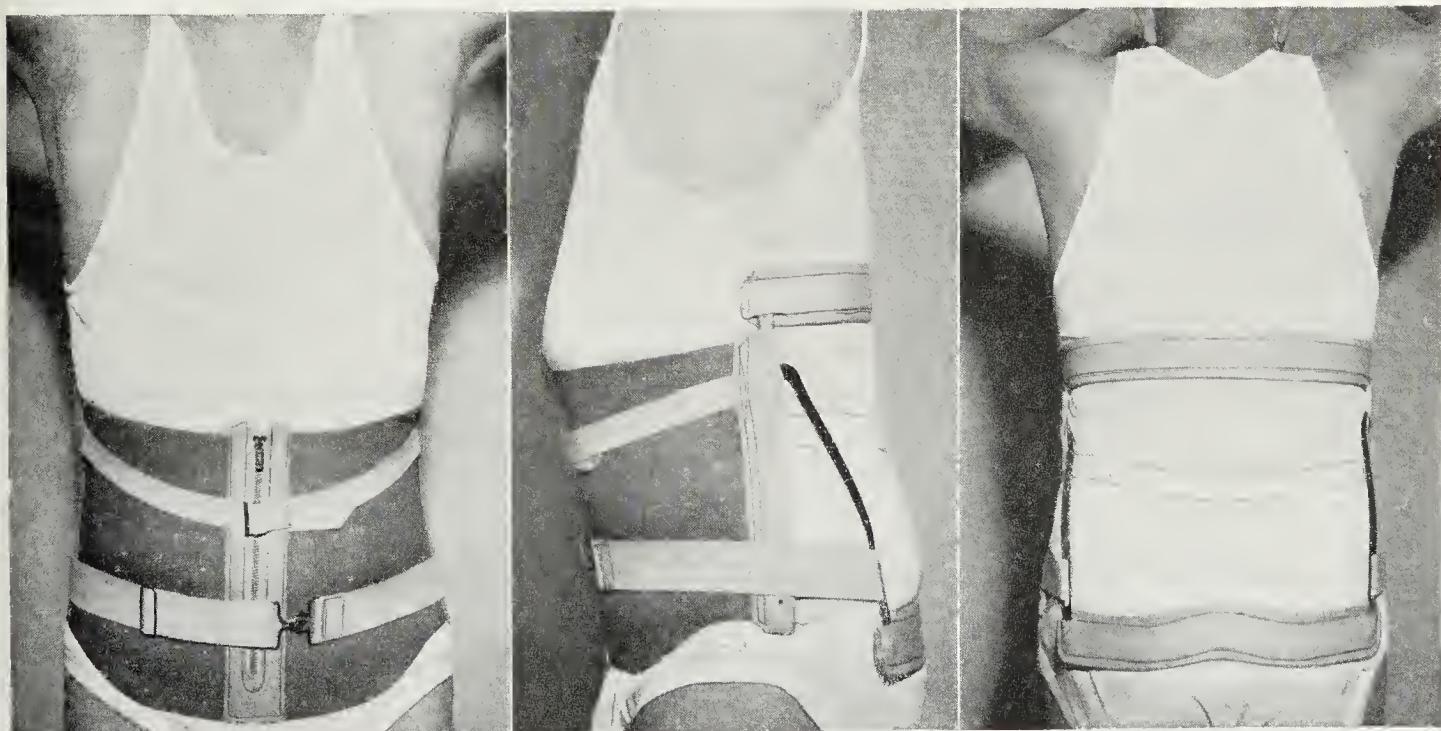


FIG. 18. Various views of a lumbar-sacral flexion brace.

A flexion plaster of Paris jacket can be used to advantage in certain chronic cases where the patients are unable to habituate themselves to correct postural principles. It should not be used until the patient has restored practically full flexion to the lumbosacral spine. The cast is applied with the patient standing and bent forward with his elbows resting on a table at approximately waistline height. After application it is cut vertically in front, removed, and dried. The cut edges are then bound and it is reapplied and pulled together by means of a belt. The patient is instructed to remove it at night and to take his exercises after removal and before reapplying in the morning. This jacket is worn from two to six weeks, as indicated in the particular case.

Acute cases should be admitted to the hospital and placed in position of flexion as shown in figure 17. Eight to 10 pounds of skin traction is applied to the painful extremity in such a way that it can be released for exercises. Medication should be directed at relieving pain and muscle spasm. The patient is instructed in exercises 1, 2, and 3, figure 15, to be taken in bed at the end of every hour when awake. In starting, each exercise is executed 10 times. The number is increased daily as tolerated. Traction is allowed to remain five to seven days. The length of time required to relieve acute symptoms depends on the severity of the case. The average case requires 10 to 14 days. When acute symptoms have subsided, a complete postural program is instituted and the patient is treated the same as the chronic case. Occasionally, when recent symptoms have been severe, a plaster of Paris flexion jacket is applied before the patient becomes ambulatory in order to avoid exacerbation during the remaining convalescent period.

If, after three weeks, symptoms are unrelieved or unimproved, myelograms are made and, whether or not a defect is apparent, operation is advised. However, those who refuse operation usually get relief over a period of months by continuing on a conservative program as outlined. This is true even in the presence of a myelographic defect. Complete relief in severe cases may not be obtained until after 8 or 10 months of faithfully following the conservative program. It is not uncommon after such a period of time to see reflexes, sensation, and motor changes return to normal, and there is increasing evidence that

repeated myelograms in many cases fail to reveal the previous defect.

It is reasonable to believe that a herniated nucleus pulposus, like other body tissues which have lost their function, undergoes absorption. One would expect such absorption to be rapid in youth, when the nucleus is of a semigelatinous consistency, but slower in middle life, when it has taken on a more fibrous character.

There are several prevalent views regarding the surgical procedure indicated in these cases. It is not the intention of the writer to discuss the merits of any particular surgical phase. It is evident that protruding nuclei pulposi, subluxated facet articulations with overstretched joint capsules, degenerative joint changes, and nerve root compressions and adhesions may all play a part in the production of pain. Except in selected cases it is folly to remove one painful factor and allow others to remain. Each case should be studied individually and the surgical program planned accordingly.

Occasionally an Ober fasciotomy can be employed to good advantage in those who present a marked tautness of the tensor fasciae latae. This procedure should be advised not as a cure but rather as an aid in reducing the lumbosacral extension.

Manipulations, injections, and physiotherapeutic measures too numerous to relate have been described. Many of these procedures are of value and are employed in connection with flexion principles. Manipulations directed at forcefully flexing the lumbosacral spine are favored. However, when done under anesthesia one should be conscious of the danger of producing a compression fracture of a vertebra.

**CERVICAL SPINE.** A collapsed intervertebral disk of the cervical spine is a common cause of pain. The usual history is similar to that of a like lesion of the lumbosacral spine.

Recurrent attacks of pain described as "catches" or "cricks" in the neck, eventually accompanied by pain radiating into the upper chest, shoulder, and down the arm, constitute a common history. The pain distribution is segmental in character and dependent upon the nerve root involved. Exposure to cold is frequently related as an initiating factor in this condition.

The usual history in chronic cases lacks acute episodes and the pain may or may not radiate

into the arm. Symptoms are usually continuous, but affected by positions.

Again, as in the low back, a careful analysis will reveal that symptoms are usually aggravated by extension. Any violent or prolonged contraction of the antigravity muscles of the head when the latter is tilted but slightly forward results in compression of the posterior structures of the cervical spine and is likely to cause acute symptoms. Typical causes of such a condition are: prolonged driving, watching a football game, bumping a car in front.

An important diagnostic finding is the increase of pain caused by passively forcing the neck into a position of combined extension and lateral flexion to the affected side. Numbness as well as pain is frequently experienced in the arm and hand from the manipulation and is usually indicative of a disk change.

Any or all of the following findings may be presented: limited cervical motions, spasm of the neck muscles, reflex and sensory changes, and occasionally partial paresis of the muscles of the forearm and hand.

The x-rays may show the following changes: narrowed intervertebral joint space most frequent between the fifth and sixth or the sixth and seventh cervical segments, marginal lipping of the adjacent surfaces of the involved vertebral segments, subluxation and degenerative arthritis of the adjacent facet articulations, and myelographic defects.

It is well to take the lateral studies in both flexion and extension in order that a luxation may be ruled out, since a luxation is treated in extension rather than flexion as is the collapsed intervertebral disk.

The conservative treatment is based on strengthening the flexor muscles and stretching the extensors as well as restoring full motion to the cervical spine.

Acute or severe chronic cases are placed in 4 to 6 pounds of cervical traction. This should be adjusted so that the neck is in mild flexion, and the extensor muscles are under stretch. The patient is instructed to remove the traction every two hours and from the supine position to flex the neck until the chin approximates the chest, then lower the head back to the pillow. The exercise should be repeated 10 times and the traction then reapplied. When acute symptoms have subsided, which usually requires four to

five days, in addition to the exercise already described, the patient is instructed to take the following exercise: From the supine position the neck is flexed until the chin contacts the chest. The head is then rotated to one side as far as possible and then to the other side as far as possible, and then back to the midline and dropped back to the pillow for rest. It is important that the chin stay close to the chest and that extension of the cervical spine when at the extremes of rotation be rigidly avoided.

At first this exercise is usually strenuous and moderately painful, but these factors are soon overcome. In starting, it is repeated three consecutive times. The traction is reapplied following the exercise and the patient remains recumbent 7 to 10 days.

Those lacking the acute symptoms are treated by the exercises alone repeated twice daily. They should not be taken except in the supine position, and should be continued indefinitely if recurrent attacks are to be avoided. Heat and light massage are valuable adjuncts in the treatment of all cases.

Immobilization by braces or collars usually affords relief of acute symptoms, but prolonged fixation contributes to limiting motion further, and this in turn prolongs symptoms. In the writer's experience, it is important to restore motions and develop a proper muscular balance between the opposing flexor and extensor muscles.

Operation is rarely necessary, since many carry a collapsed intervertebral disk for years without symptoms. Surgery is indicated in cases of persistent disabling symptoms after a prolonged conservative program has failed to give relief. Such cases should be studied by myelograms and the operation indicated instituted. The writer favors a fixation by fusion of the altered arthritic joints as well as the removal of the interfering disk substance in order to avoid future disability.

**Sacroiliac Strain.** It has become apparent that a sacroiliac strain, either acute or chronic, is a far less common cause of the painful back than has been the general consensus in the past. However, the present inclination to ignore it completely is incorrect. Not infrequently this condition is encountered and must be dealt with as a definite clinical entity. There is no unanimity of opinion as to what constitutes a differential diag-

nosis of a sacroiliac and a lumbosacral lesion. The confusion is probably due to the fact that the patient who has a painful sacroiliac joint also has a collapsed lumbosacral intervertebral disk. This is because the force that produces a strain of the sacroiliac joint is the same one that causes an abnormal compression of the posterior portion of the lumbosacral intervertebral disk. The disk usually collapses under the strain before the same force on the sacroiliac joint has become of clinical significance. It is, therefore, probable that both lesions are playing a part in the production of symptoms in many cases.

The best clinical picture of an acute sacroiliac strain is seen in the patient who has a satisfactory lumbosacral fusion. A few such cases have been studied. The cause most frequently related is that of lifting a load while in the erect attitude. These patients complain of severe pain in the hip which radiates down the back of the thigh to the knee, but not below, and is aggravated by weight bearing. They usually present a spinal list to the unaffected side, and stand favoring the affected extremity. Major tenderness to pressure is localized over the inferior border of the sacroiliac joint. The sciatic nerve at the notch is not tender to pressure. The hamstring muscles are usually in spasm. Spinal motions are limited by protective spasm. The extremes of all hip joint motions on the affected side increase pain. The straight leg-raising test is limited by protective hamstring spasm.

Chronic strain of the sacroiliac joint is seen more frequently than acute strain. It differs from the acute in that both joints, as a rule, are involved. It is encountered most frequently in thin, young adult females who have a tendency to present a poor muscular tonus and loose joints.

Eliminating the chronic lumbosacral symptoms which are usually associated, the frequent complaint is that of pain which originates in both hips and radiates down the back of both thighs. Symptoms are worse just preceding the menstrual cycle and are usually aggravated by weight-bearing activities. An elastic girdle is usually worn for comfort.

Aside from the constitutional factors already mentioned, the findings are those of localized tenderness over the inferior border of the sacroiliac joints and a complaint of pain referred to the sacroiliac joint on the extreme of all hip joint motions.

The x-rays fail to reveal any changes of significance in those cases experiencing an acute sacroiliac strain. In the case presenting chronic symptoms the x-rays reveal an abnormally wide joint space with hypertrophic lipping at the inferior border of both joints. The extreme mobility of the sacroiliac joints occasionally can be demonstrated by an x-ray of the symphysis pubis. Two anteroposterior exposures are necessary and are taken with the patient in the weight-bearing position. The first is taken with the weight borne on one leg and the second with the weight borne on the other. This technic has been described by Chamberlain.

The treatment of an acute sacroiliac strain consists primarily of rest in a recumbent position. The thighs should be flexed to an angle of approximately 45 degrees. Heat, massage, and a pelvic binder may be valuable adjuncts. A relief of symptoms usually is obtained after a period of 10 to 12 days.

Those experiencing chronic symptoms are advised to wear a pelvic binder and to increase weight-bearing activities in an effort to strengthen the ligamentous structures. The usual sacroiliac belt, due to its bulkiness, is unsatisfactory in treating women. The use of a panty girdle with the upper half turned down so that there is a double binding around the pelvis is far less objectionable and usually more effective in relieving pain. In addition to the pelvic binder and increased weight-bearing activity, a postural program directed at reducing the lumbosacral angle is indicated in most cases. Such a program has been described under the heading Intervertebral Disk Changes.

In rare cases where symptoms cannot be controlled by conservative means and an abnormal range of motion can be demonstrated, a surgical fusion is indicated, providing the lumbosacral spine has been given its due consideration.

## EXTRASKELETAL LESIONS

### NEUROGENIC LESIONS

**Spinal Cord Tumors; Tumors of Cauda Equina.** The painful back is caused more frequently by tumors of the spinal cord and cauda equina than by any other single neurogenic lesion. Other causes may be multiple sclerosis, syringomyelia, arachnoiditis, myelitis, tabetic neurosyphilis, epidural abscess, subarachnoid

hemorrhage, extradural cysts, and other less common neurogenic lesions.

Spinal cord tumors, as a rule, cause early constant and severe pain in the back. The pain is not altered greatly by position or movements. The unusual complaints, actions, and pleadings for relief in some cases occasionally result in a hasty diagnosis of hysteria or drug addiction. Most cases present root pains which may suggest cardiac, kidney, gastrointestinal, and other visceral diseases, as well as pains in the extremities closely resembling those of the intervertebral disk syndrome. Muscular weakness, clumsiness, changes in sensation, and disturbances in sphincter control and sexual functions are common complaints.

In most cases the diagnosis can be made by the usual sensory and motor tests together with the Queckenstedt test and a myelogram.

Surgical removal affords the only chance of cure.

A tumor of the cauda equina frequently presents a clinical picture very similar to that of a spinal cord tumor, although the pain in the perineum is likely to be more severe than is that in the back. The condition is characterized by progressive motor, sensory, and sphincter paralysis and a gradual loss of reflexes. In early cases the findings may be similar to those of a peripheral nerve disease, especially as seen in nerve root compression caused by a herniated nucleus pulposus.

Here, as in spinal cord tumors, treatment other than surgical removal is of no avail.

### PARIETAL LESIONS

**Muscle Strain; Fibrositis.** It is the opinion of the writer that the diagnoses of muscle strain and fibrositis in connection with the painful back are too frequently used as a covert. Such diagnoses should be made only after careful and complete studies. Muscular spasm with associated pain, so frequently diagnosed in the past as a muscle strain, usually represents nature's means of splinting a painful skeletal lesion. It is probable that a painful condition of the fibrous tissue may develop as a result of long-continued muscle fixation or contraction. If so, it represents a symptom rather than a cause.

Until the clinical and pathologic pictures are better understood, one should look further for an explanation of the painful back.

### VISCERAL LESIONS

The pain experienced in the back as a result of a visceral lesion is referred pain. Referred pain is pain experienced in one part of the body separated from the offending lesion but having a common segmental innervation. For this reason, referred pain usually is in the same general location except where a visceral organ and an adjacent extremity are innervated by the same segment.

Classic examples of referred pain are pain in the left arm accompanying a cardiac lesion and pain in the inferior right scapular region accompanying a gallbladder disorder. Its importance has been overemphasized in its relation to the painful back. Most cases experiencing a referred pain in the back relate other symptoms referable to the primary site of pathologic change which dominate the clinical picture. This is especially true of pelvic and genitourinary lesions. The most confusing cases are those which have a visceral lesion within the pelvis that acts as an aggravating factor to an already existent mechanical lesion of the spine. This relationship is well demonstrated in the female with a lumbosacral lesion who always experiences an increase in pain in the lower back just preceding the menstrual cycle. A low-grade prostatitis and uterine displacements rarely cause pain in the lower part of the back in the absence of a spinal lesion. The same is not true in viseeral lesions causing acute symptoms. The complaint of diffuse pain in the back is frequently severe in coronary thrombosis, renal calculi, acute gastrointestinal infections, acute pelvic infections, neoplasms, etc.

In the presence of such lesions, the spine as the source of the complaint usually can be ruled out by a simple examination of the nude back. A localization of tenderness by means of pressure and percussion is the most important differential clinical means. Light jarring with the ulnar aspect of the fist and pressure with the palmar aspect of the thumb to the spinous process of each vertebral segment will localize major tenderness to a definite segment if the source is within the spine. If not, such a localization cannot be made. A jar applied to the sacrum of a person with an acute lesion within the pelvis will elicit the complaint of pain. The same is true at the lumbodorsal level with a neoplasm of the pancreas or an acute lesion of the kidney, but, on questioning, the patient will volunteer the infor-

mation that the pain experienced is deep and cannot be localized to the immediate underlying bony structure. Another valuable differential point is that referred pain usually is relieved by pressure, while pressure applied over a lesion of the spine increases pain. Muscle spasm and limited spinal motion may be present in either, but is less frequent in acute visceral disturbances than in acute lesions of the spine.

#### MAXILLOPHARYNGEAL INFECTION

**Focal Infections.** The absorption of bacterial toxins from foci of infection within the oral cavity, pharynx, sinuses, or elsewhere, except in cases of rheumatoid arthritis and rheumatoid spondylitis, is rarely if ever the primary cause of the painful back. It is not uncommon to see low back pain with sciatic radiation relieved by the removal of infected tonsils or abscessed teeth. However, the majority of such cases will be found to have a collapsed intervertebral disk in the lower spine and eventually will experience a recurrence of symptoms in the absence of any demonstrable focus of infection. An infection should be considered as a secondary aggravating factor and should be removed whenever its presence is definite.

Infectious lesions of the nasal and paranasal cavities, especially those in the posterior two thirds which drain principally through the deep cervical lymph glands, are a fairly common cause of pain in the neck and shoulders. The pain is probably the result of a protective muscle spasm aimed at splinting the part, since the painful nodes are further irritated by motions of the neck.

In the writer's experience, the pharyngeal tonsil has been found to be a common offender. This is especially true in those cases where it has been removed in early life.

The history related is that of a gradual onset of pain in the neck and shoulders persisting over a period of weeks or months and aggravated by motions of the neck. Patients frequently complain of "painful knots" in the back of the neck which they can palpate at times, and they state that their pain is more severe at such times.

The examination reveals swollen occipital and inferior deep cervical lymph glands which are painful to pressure. A protective spasm of the cervical muscles is present. If the involvement is unilateral, rotation and lateral flexion to the opposite side are limited and painful; if bilateral, all motions of the cervical spine are so affected.

X-ray studies fail to reveal any pathologic change within the cervical spine.

Treatment consists of removal of the infection.

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# 6

## Pain in the Extremities

Eugene A. Stead, Jr.

### Introduction

Disturbances Within the Tissues of the Extremities  
Irritation of Sensory Nerves and Roots, and Lesions in  
Spinothalamic Tract and Thalamus  
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Causes of Pain in the Extremities  
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Pain from Ischemia, Thrombosis, Embolism, and Arteritis  
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sure on Nerves or Nerve Roots  
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Approach to the Patient with Pain in the Extremities

### INTRODUCTION

Pain in the extremities comes from (1) disturbances within the tissues of the extremities, (2) irritation at any level of the sensory nerve paths serving the extremity, or (3) pain referred from deep somatic or visceral structures.

### DISTURBANCES WITHIN THE TISSUES OF THE EXTREMITIES

Any lesion causing inflammation, swelling, ischemia, or destruction of pain-sensitive tissues of the extremity may cause pain. Burns, frostbite, and chemical injuries are painful. Arthritis, cellulitis, abscesses, osteomyelitis and hematomas, tumors, Paget's disease, and bone changes with hyperparathyroidism cause varying degrees of pain. Degeneration of nerves and trauma to nerve trunks are painful. Damage to nerves or to muscles from ischemia is painful.

### IRRITATION OF SENSORY NERVES AND ROOTS, AND LESIONS IN SPINOthalamic TRACT AND THALAMUS

Involvement of the nerves from the time they pass from the extremity until they reach the spinal cord may cause pain in the extremity. The pain of cervical rib, ruptured intervertebral disk, spinal cord tumor, and tabes dorsalis falls into this group. Central pain from involvement of the spinothalamic tract and thalamus is occasionally seen.

### PAIN REFERRED FROM DEEP STRUCTURES

The pain of angina pectoris and myocardial infarction frequently radiates to the inner surfaces of the arms. Pain from the hip may be referred to the knee. Pain from the deep muscles of the back or from the vertebrae may be the source of pain referred to the extremity.

### CAUSES OF PAIN IN THE EXTREMITIES

**1. Pain from Trauma, Inflammation, and Swelling.** The immediate response to trauma is due to mechanical stimulation of nerve endings. Pain persisting after the injury may result from chemical stimuli produced by the injured tissues. Lewis has described the reactions in skin made hyperalgesic by injury. Needle pricks too light to awaken pain in uninjured skin will arouse a response in traumatized areas. Pain is easily induced by friction or warming, and often by cooling. Distention of the skin by direct stretching or by venous congestion causes pain. If injured skin is rubbed, pain is felt immediately; this subsides and is followed in about 15 seconds by a second pain which lasts one or more minutes. If the circulation to the part is obstructed, the initial pain is unaltered, but the second pain rises to a greater intensity and persists until approximately one minute after the circulation is restored. The first pain comes from direct stimulation of sensory nerves, the second from a relatively stable pain-giving substance released into, and held within, the tissue space. The chemical nature of this substance is not known. Skin made hyperalgesic by injury, regardless of the mechanism of the injury, will respond to heat and congestion with burning pain. If this reaction occurs diffusely in the skin of the extremities without obvious cause, the burning pain from warmth and congestion is called erythromelalgia.

The injury to the skin caused by heat is well

recognized. That prolonged cold will cause tissue damage in many ways comparable to burns is less commonly realized. Prolonged immersion of the feet, or prolonged exposure to cold with the feet in wet boots, will cause severe tissue damage to the point of gangrene, even though actual freezing does not occur. Freezing, of course, causes tissue damage and may produce gangrene. Fibrosis and ischemic neuritis are common after any form of injury from cold, and may cause persistent tenderness and pain.

In bacterial infections, the mechanical factor of rapidly forming edema increases local tissue pressure, and causes pain in skin already made hyperalgesic by chemical factors associated with injury. Congestion aggravates the pain and elevation of the part alleviates it. Less rapid edema formation usually does not cause pain because the tissues stretch gradually. Patients with cardiac edema complain of heaviness of the legs and occasionally of diffuse tenderness. Edema associated with varicose veins may cause a sense of fullness and dull ache. In acute thrombophlebitis, pain may arise from the involved veins. It may be aggravated by ischemia secondary to sympathetic vasoconstriction resulting from the sensory stimuli from the inflamed veins. Tumor masses may cause pressure on bone or peripheral nerves.

Arthritis is a common cause of pain in the extremities. Paget's disease and pulmonary osteoarthropathy are less common causes of bone pain.

The syndrome of sore, painful shoulder with superficial and deep areas of exquisite tenderness is common. It frequently begins as wryneck, and at times occurs in a number of persons closely associated with one another. Marked spasm prevents abduction of the arm at the shoulder. The entire upper extremity may feel numb and queer. There is no fever. Biopsy of the skin and muscles shows apparently normal tissues. Light freezing of the skin with ethyl chloride or procainization of the superficial and deep tender areas frequently gives dramatic relief of pain which may be permanent. The mechanism of pain production in this syndrome is not known.

**2. Pain from Ischemia, Thrombosis, Embolism, and Arteritis.** Interference with blood supply may result from obliterative arterial disease or embolus, or from arteriolar spasm secondary to stimulation of sensory receptors or nerves. It may be aggravated in polycythemia by the adverse effect of increased viscosity of the blood.

The pain may be produced by the action on sensory nerve endings of metabolites accumulating in the muscles or by changes in the nerves themselves.

The sensations produced by ischemia to the extremity are familiar to all. When the blood supply is occluded, the part gradually becomes numb and paralyzed and we say the part has "gone to sleep." If the part is not moved, pain does not develop. The sensation at the end of the fingers becomes dulled in about 12 to 15 minutes. At that time, light pressure on the fingers may hurt, and stroking the finger tips causes an unpleasant sensation. Later pain is dulled, and much later analgesia develops. On release of the arterial occlusion, unpleasant tingling occurs, particularly in the fingers. This tingling is not the result of the inrush of blood into the fingers, because it occurs if blood is released only into the proximal part of the extremity. It results from changes in the main nerves of the arm during recovery. Stroking the fingers accentuates it. The paresthesias produced by the injury and recovery of the nerve from ischemia are similar to those produced by chronic disease processes involving the peripheral nerves or nerve roots.

If the extremity is exercised while the circulation is completely occluded, a continuous diffuse aching pain develops in the muscles because the sensory nerves are stimulated by the formation of stable metabolites. The pain is present during and between contractions. It is frequently described as a cramp, but the muscles are flaccid. If the contractions are continued, the muscles become tender. On release of the tourniquet, the pain disappears in a few seconds, probably as the result of the carrying away of readily diffusible metabolites.

If the brachial artery at the elbow or the femoral artery at the inguinal ligament is occluded by digital pressure for one-half hour, instead of by application of a cuff, much less change in the circulation occurs because collateral circulation is not stopped. Loss of sensation does not occur and, on release of the occlusion, the reactive hyperemia is much less intense than with the cuff.

In occlusive vascular disease of the vessels of the legs, a common symptom is pain with tenderness of the muscles which is relieved by rest. It is called *intermittent claudication*, and represents in the extremity muscles the same changes which occur in the heart with angina pectoris. The rest-

ing muscle is receiving an adequate supply of blood for normal metabolism. When muscle metabolism is increased by exercise and occlusive vascular disease prevents increase of the blood supply, metabolites accumulate in the muscles and stimulate the sensory nerve endings. The nature of the chemical substances has not been determined. The more severe the circulatory impairment, the less exercise is required to produce the pain and the more slowly the pain disappears on rest.

In occlusive vascular disease, the nerves themselves may become ischemic and cause severe and persistent pain. This pain, in certain instances, is aggravated by dependency because of stimuli resulting from congestion. In addition to Buerger's disease and arteriosclerosis, ischemic neuritis is a prominent symptom in small-vessel involvement of the type seen in periarteritis nodosa.

Embolus or thrombus in the brachial or femoral vessels frequently produces sufficient circulatory impairment to cause pain. The pain in thrombosis is indistinguishable from the pain of embolism. The pains do not occur at the site of occlusion but in the muscles and tissues distal to it. The time of onset of the pain will depend on the temperature of the part, the amount of activity, and the amount of associated vasospasm. If the part is warm and still, the limb may become numb before the muscle pain is produced. Heat applied to a limb with poor circulation may cause gangrene from (1) increased metabolism of tissue without corresponding increase in blood supply, or (2) lack of cooling effect of the blood. When heat above body temperature is applied to the skin, the blood normally acts as a cooling system; in the presence of arterial occlusion, local heating causes an immediate rise in temperature of the part. If the part is exercised, the muscle pain occurs early. Twenty-four hours after an embolus has lodged, the vessel wall may be tender because of periarterial inflammation. Occlusion of small blood vessels does not cause pain unless ischemia of muscle or nerve is produced.

Normal skin hurts when warmed after severe exposure to cold. This is a response to direct injury from the cold. The white, cold fingers in Raynaud's phenomenon may be painful. In scleroderma the thickening of the connective tissue combined with spasm of the digital arteries may result in painful ulceration of the fingers and eventual loss of the terminal phalanges.

The pain from ischemia or infection is frequently altered or absent in patients with diabetes because of associated peripheral neuropathy. Whenever a painful looking lesion of the extremity is treated casually by the patient, neuropathy should be suspected. Tabes dorsalis, leprosy, senile cortical atrophy, and syringomyelia should be considered.

The circulation to the extremities can be greatly modified by overactivity of the sympathetic nervous system. In many instances of injury, inflammation, or thrombophlebitis, sensory stimuli arising in the extremity may produce intense reflex vasoconstriction, and the resulting ischemia may cause diffuse pain. Relief of the vasoconstriction by paravertebral procaine block of the appropriate sympathetic ganglia may cause striking relief of pain. Similarly, sensory impulses arising from ischemic areas after arterial occlusion by an embolus or thrombus may stimulate sympathetic nervous system activity and reflex spasm. Paravertebral block will relieve the spasm of collateral vessels and, if circulation improves sufficiently, pain will disappear.

**3. Pain from Neuropathy, Neuritis, Ganglionitis, and Pressure on Nerves or Nerve Roots.** Involvement of the peripheral nerves frequently causes unpleasant sensations in the extremities. In diabetic neuropathy, numbness may be accompanied by diffuse pains through both lower extremities. Any combination of sensory loss and pain may occur in peripheral nerve damage from infection, poisons, or mechanical factors such as trauma or pressure. Spinal cord tumors and slipped intervertebral disks are common causes of nerve root pain. Inflammation of the dorsal root ganglions results in the syndrome of herpes zoster. The redness and blistering is attributed to antidromic vasodilatation from stimulation of the sensory nerves. Impulses arising in sensory nerves or ganglions and passing peripherally to the sensory end organs are called antidromic. Involvement of the dorsal root ganglions, dorsal roots, and adjacent spinal cord produces the lightning pains in the extremities typical of tabes dorsalis. Paralysis from pressure in the axilla may be caused by crutches or by sleeping with the arm thrown over the back of a chair. The latter usually occurs in alcoholic stupor and is called "Saturday night paralysis."

**4. Pain from Immobilization, Spasm, and Cramps.** Prolonged immobilization of a part re-

sults in stiffness of muscles and joints. The muscles tighten and splint the joint, and motion is prevented. An attempt to move the part produces pain. Local infiltration with procaine will frequently allow a great improvement in motility, which may be permanent. Similar spasm occurs after trauma. A painful sprain of the ankle which prevents walking may be relieved in a few minutes by procainization. Even in acute arthritis part of the pain may be secondary to spasm and may respond to curare or procaine, which relaxes the muscle. In acute poliomyelitis, non-paralyzed muscles may be sore and contracted. Application of hot packs gives relief.

Muscles placed in unusual positions may go into intense contraction and cause severe pain. Cramps in the foot or leg occurring at night are common. These are relieved by forcefully extending the joint so as to stretch the cramped muscles. In nocturnal cramps, pain occurs so quickly that simple ischemia would seem unlikely. They differ from the cramps of arterial disease in that the pain is not brought on by exercise. Painful muscle cramps occur in tetany and in chloride deficiency. Whether the pain of tetany is caused by ischemia from the prolonged contraction, or related to damage because of the intensity of the contraction, is not known.

Unaccustomed, strenuous exercise causes aching, tender muscles, tendons, and joints. The pain results from low-grade injury to the muscles from repetitive maximal contractions.

**5. Glomus Tumor.** Tumor of the glomus, the specialized arteriovenous anastomosis of the skin, produces unusual vasomotor phenomena and radiating pain. It is characteristically a small (a few millimeters in diameter), extremely painful, purplish nodule either in the skin of the extremity or under the nail. Pain is caused by contact or change of temperature, and may spread to involve the entire extremity. The reason these tumors are so painful is not clear. While most observers have noted an unusually rich nerve supply, others have not found it.

**6. Pain from Causalgia.** Pain in the extremity associated with signs of local circulatory dysfunction is seen in nerve injuries after amputations and in persons with coronary arterial disease with or without myocardial infarction. It occurs in the hand-shoulder syndrome. The above conditions have one thing in common: Local injury sets up a reaction which at first appears to be the result of

sensory stimuli from the injured part. Later changes occur in the peripheral nerves, spinal cord, or central nervous system so that the process continues after the injury has apparently healed.

a. **CLASSIC CAUSALGIA.** Injury to any nerve, more commonly the median or sciatic nerve, may give rise after a few days or weeks to a burning pain. The gross injury to the nerve may have been severe or trivial. The pain will be caused by light friction, and deep pressure is less painful. Heat usually provokes the pain. The skin becomes smooth and glossy and is frequently wet with sweat. It has a red or purplish tint. The temperature of the involved part is usually said to be increased. The pain is frequently relieved by sympathectomy. Causalgic pain may result from the activation of sensory fibers by sympathetic impulses. If injury links the two systems in such a way that leakage of efferent sympathetic impulses into the sensory nerves can occur, most of the clinical phenomena of causalgia, including the relief by sympathetic block, can be explained.

The initiating mechanisms of causalgia are unknown. Several theories have been advanced: (1) The sensitivity of the skin may result from vasodilator substances released by repeated centrifugal impulses arising in the injured area. It is known that stimulation of the paralyzed end of a cut cutaneous nerve results in vasodilatation which may be accompanied by itching and burning pain. (2) The sensitivity of the skin may result from a summation of impulses from normal skin with those from the injured nerve.

Regardless of the local mechanism, it appears that other mechanisms central to the extremity are capable of continuing the process once the causalgia has been present for some time. At this stage, dorsal root section or sections of the spinothalamic tract may not modify the pain. Chain reactions within the short interconnecting nerves in the spinal cord have been postulated. Paravertebral block or sympathectomy should be done early before these central changes occur and before the patient becomes a drug addict. Because the patient's complaints are so bizarre and because the original injury may be mild, causalgia is frequently mistaken for a compensation neurosis.

b. **PHANTOM LIMB PAIN.** After amputation, the patient may complain of pain which he localizes in the removed part. At times this may be

caused by a neuroma of the cut nerves or by the faulty construction of the stump. The stump may show vasomotor changes. In most instances, therapy directed toward the stump does not relieve the pain; at times, paravertebral block of the sympathetic ganglions does. The clinical observations suggest that, as in causalgia, pain may begin locally, but that changes may take place in the central nervous system which are responsible for its continuation.

c. HAND-SHOULDER SYNDROME. Myocardial infarction is frequently complicated by persistent shoulder pain with marked limitation of motion. At times, swelling of the hand and wrist and contraction of the palmar fascia are present. The elbow is not involved. Atrophy of skin and osteoporosis may follow. Similar disturbances in shoulder and hand function have occurred in association with trauma, hemiplegia, herpes zoster, and cervical osteoarthritis. This syndrome may occur without recognized associated diseases. The exact mechanism of this fairly common syndrome is unknown.

#### APPROACH TO THE PATIENT WITH PAIN IN THE EXTREMITIES

A careful history will usually yield important clues. The pain may be felt in the region of the knee when the disease is in the hip, or in the foot when the knee is the seat of the disorder. Pain on first arising in the morning, and particularly when associated with stiffness, suggests a disturbance of joints or muscles. When the bone is affected, there is commonly nocturnal aggravation. Pain of throbbing character usually arises in tense tissues with free blood supply, and hence suggests bone as the source. Sharp shooting pain

of brief duration, brought on by coughing or by sneezing, is common with disorders of the vertebral column or of the posterior nerve roots. Relief of discomfort by elevation suggests venous obstruction; relief by dependency suggests an arterial lesion. Pain ascribed to walking may actually be due to standing, and may have its source in the feet. Pain due to ischemia of muscles is characteristically induced by walking, with latency of onset and of offset. Disorders of joints are likely to be accompanied by pain on local movement, the duration of the discomfort paralleling that of the movement.

The history having suggested the responsible structure, the suspicion is confirmed or disproved by the physical findings and the appropriate special procedures. Since these are mentioned in the later chapters dealing with the disorders of the various systems of the body, they need not be cited here. However, it should be emphasized that x-ray examination, while often invaluable in the case of long-standing disease of the bones, may be entirely negative in the presence of serious skeletal disorders of recent origin. This is especially important in regard to acute osteomyelitis, and to the earlier stages of metastatic neoplasms of bone.

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## Lassitude, Asthenia, and Syncope

T. R. Harrison

### Persistent Weakness

Lassitude

Asthenia

### Recurrent Weakness and Syncope

The More Important Causes of Recurrent Faintness and Syncope

Differential Diagnosis

The term "weakness" is used by patients to describe a variety of subjective complaints which vary in their prognostic significance and in their import. Most of the subjective disorders included in this term will be found, on careful questioning, to fall logically within the following classifications:

#### I. Persistent Weakness:

A. *Lack of energy, lassitude, listlessness, malaise, and undue fatigability:* These terms, while not synonymous, shade into each other, and are all characterized by loss of that sense of well-being which is typically found in persons who are healthy in both body and mind. Symptoms of this type are present in a large proportion of all patients, and have little diagnostic significance unless they constitute the presenting complaint. For the sake of brevity this group of complaints will be considered together under the term *lassitude*.

B. *Loss of muscular strength may be either:* (1) local, involving specific muscle groups (palsy, paralysis); or (2) general, involving the entire musculature (asthenia). (A discussion of paralysis lies outside the scope of this chapter.) The generalized type of muscular weakness will be considered below, under the title of *asthenia*, which is less common than lassitude and more likely to indicate serious disease.

II. Recurrent Weakness: Many patients complain of "attacks of weakness," when careful ques-

tioning reveals that it is a diminished sense of alertness, a feeling of lightheadedness, or a sensation of faintness which is the actual symptom. Since these complaints are subjectively different from lassitude and asthenia, and since the causes are likewise different, such recurrent attacks of weakness will be discussed later.

Before proceeding with the discussion of these several symptoms it should be emphasized again that the unqualified term "weakness" is so vague as to be almost meaningless, and that its evaluation must necessarily begin by a decision as to whether the patient actually means paralysis, asthenia, lassitude, or faintness.

### PERSISTENT WEAKNESS

#### LESSITUDE

(Lack of energy, languor, listlessness)

The mechanism of this symptom, when occurring under physiologic conditions or as a result of organic disease, is unknown; possibly it is related to disturbances of cellular metabolism in the nervous system or in the muscles, but, if so, the exact nature of such disturbances remains to be elucidated. The lassitude which occurs as the result of emotional stress is intimately related to conflict within the personality. If a person is so busy reconciling within himself a myriad of fears, hates, or dissatisfactions, he will be unable to spend energy usefully in productive pursuits. Under such circumstances, lassitude, which is such a common early symptom in neuroses, reactive depression, and psychoses, is to be regarded as a distress signal from an organism laboring under unwelcome stress.

**Differential Diagnosis.** Since almost any physical or emotional disorder may be ac-

accompanied by lassitude, an attempt will be made to limit the following discussion to causes which are likely to be obscure.

*When lassitude is not the presenting symptom* (i.e., the chief complaint), the clue to the diagnosis is usually to be arrived at by investigation of the more troublesome complaints, such as fever, chills, loss of weight, pain, cough, dyspnea, etc. Thus, in subjects with acute infections, in patients with malignant neoplasms, and in many individuals with almost any type of serious disease, the other symptoms are in the foreground and are much more likely to have diagnostic significance than is the associated lassitude.

*When lassitude is the presenting symptom*, the possible causes are less numerous. Perhaps the most common cause in such instances is an emotional disturbance, such as that which so commonly leads to depression, anxiety states, and other neuroses; but since psychic and somatic disorders frequently coexist, it is wise to search for organic disease before concluding that the symptom is entirely psychogenic. The search should be thorough but prompt, since unnecessary waste of time may tend to aggravate an anxiety state, if present. At the same time the patient should be observed for positive evidence of an emotional disorder, and if such evidence is found or if the diagnosis remains obscure, psychiatric consultation is desirable. The importance of thorough but immediate observation cannot be overemphasized.

*Postinfectious lassitude* is frequent following almost any type of severe, acute febrile illness. The symptoms are very similar to those of psychogenic lassitude: fatigue, palpitation, listlessness, and irritability are commonly present, and in many instances emotional factors play an important or dominant role. Otherwise, the condition clears up within a few weeks or, rarely, a few months after the acute infection has subsided. Experience gained during the recent war indicates that prolonged rest in bed delays disappearance of postinfectious lassitude, except in the case of infectious hepatitis.

*Obscure chronic infections* are responsible for lassitude in many instances. Almost any chronic infection may be causative, but perhaps the most common ones (in the United States) are tuberculosis, rheumatic fever, and certain diseases such as subacute bacterial endocarditis and chronic

pyelonephritis due to relatively avirulent bacteria, and certain parasitic infestations such as malaria and hookworm. The frequency of brucellosis as a cause of lassitude and low-grade fever is uncertain. Unfortunately, there is no reliable method (other than the blood culture, which is rarely positive in chronic cases) of diagnosing this condition.

*Anemia* (Chapter 22), when moderate to severe, and regardless of cause, is likewise frequently responsible for lassitude. The severity of the symptom is more likely to parallel the hemoglobin level of the blood than the number of erythrocytes.

*Metabolic and endocrine disturbances* (Chapter 52) of various types may produce lassitude. The symptom is likely to be extremely marked, to be associated with true muscular weakness, and to dominate the clinical picture in Addison's disease and in Simmonds' disease, both of which, of course, are rare disorders. In persons with *hypothyroidism* with or without outspoken myxedema, lassitude is usually pronounced. It is present in many patients with *hyperthyroidism*, although often less troublesome than the associated nervousness. Any type of nutritional deficiency may, when severe, produce lassitude. In the earlier states this may be the only complaint, since objective findings may be absent in many cases, and the only clues as to the underlying disorder may come from the complaint of languor and the dietary history, the diagnosis in some instances being established by chemical studies on blood and urine. Lassitude is commonly the initial symptom in patients with *chronic disease of the liver*, and not rarely in persons with *diabetes*. It occurs rather constantly in subjects with disorders (fortunately rare) of the parathyroid glands.

Almost any type of chronic *exogenous or endogenous intoxication* is likely to be associated with lassitude, which, however, is only rarely the chief complaint. Among the more common examples are *alcoholism*, *bromism*, *prolonged ingestion of barbiturates*, *morphine addiction*, and *uremia*.

*Emotional disorders*, whether accompanied by severe anxiety, prolonged worry, or other disturbances of psychic function, frequently lead to lassitude, and are perhaps the most common cause. The much abused term "neurasthenia"

would seem to have a valuable connotation when limited to such instances, and when applied with the understanding that it refers to a symptom—psychogenic lassitude—and does not constitute a diagnosis. Patients with "neurocirculatory asthenia" often have well-marked lassitude. When a patient presents conclusive evidence of a disturbance of the personality or of organic disease (Chapter 34), we should not be content to assume that the obvious disturbance is the sole cause of the symptom, but should search for a somatic or a personality disorder as well, remembering that the coexistence of organic and psychogenic disturbances in the same patient at the same time is a frequent occurrence, and that one of the common causes of emotional disturbance is anxiety concerning the presence of organic disease, either genuine or assumed.

There are numerous other causes of lassitude; the disorders which have been mentioned seem, however, to be the most common and important.

**Acute Lassitude.** The foregoing discussion deals with chronic and persistent lassitude, because this is the problem as it is most commonly presented to the physician. Lassitude of sudden onset is likely to be due to (1) an acute infection, (2) a disturbance of fluid balance, and especially one producing extracellular fluid deficit, or (3) rapidly developing circulatory failure of either peripheral or cardiac origin. In these various disorders, which will be discussed in detail in subsequent chapters, the subjective manifestation—lassitude—is likely to be accompanied by outspoken objective phenomena (fever, tachycardia, etc.), which dominate the clinical picture.

### ASTHENIA

(Generalized muscular weakness, debility, feebleness)

This symptom is relatively uncommon, as compared to the great frequency of lassitude. True asthenia is never due to psychogenic disorders alone, and is not likely to result from anemia or from the chronic infections, except in their advanced stages. It is observed in the terminal phases of most wasting diseases, and throughout the course of severe acute fevers. Its most common causes are senility and prolonged confinement to bed, regardless of the

underlying disease process. When asthenia is the presenting symptom in a patient who is not senile, and who has not been at bed rest, one should think of the severe forms of the common anemias, of nutritional deficiencies, of the diffuse disorders of the motor system, of the diseases of the thyroid gland, and, finally, of such rare endocrine disorders as Addison's disease and Simmonds' disease.

One not extremely rare cause of asthenia merits special attention—namely, myasthenia gravis. In this remarkable disorder the patient may have nearly normal muscular strength following prolonged rest, but quickly develops fatigue and, eventually, paralysis of the affected muscles following repeated contraction. Since the muscles supplied by the cranial nerves are especially involved, disturbances of vision, of swallowing, and of speech are usually the presenting symptoms. The disorder may be due to excessive destruction by cholinesterase of acetylcholine, which is necessary for muscular contraction. This destruction can be inhibited by cholinergic drugs such as neostigmine, and such drugs are consequently of great value in treating the disease.

When more than one member of the family is subject to recurrent attacks of weakness proceeding to the point of actual paralysis, but without loss of consciousness, and when such seizures are separated by intervals of good health, one should be suspicious of a rare disorder—familial periodic paralysis.

The distinction between lassitude and asthenia is not a sharp one, as the former symptom shades into the latter. All patients with asthenia also have lassitude, but most patients with lassitude do not have genuine asthenia. Before concluding that a person has true loss of strength rather than the more common and less serious loss of energy, one should either be able to demonstrate the muscular weakness objectively, or should obtain a story from the patient that he is no longer able to perform specific muscular acts which previously could be done readily.

The mechanism of asthenia, like that of lassitude, is unknown. Probably both symptoms are related to certain yet-to-be-discovered metabolic changes in the cells of the nervous system, or of the muscles. Although the distinction between the two symptoms is important, from the standpoint of both diagnosis and of prog-

nosis, the difference is probably quantitative rather than qualitative. Hence, in the remainder of this chapter, they will be considered under the term "persistent weakness."

*Procedure in a patient with obscure persistent weakness as the presenting symptom.* Some of the more important features which are valuable in differential diagnosis are indicated in table 4. The following points would seem to merit additional emphasis.

*The decision as to whether an obscure but active chronic infection exists* is made largely on the basis of measurements of *temperature* (preferably taken at two-hour intervals, and under conditions of activity if the resting temperatures be normal), *leukocyte count*, and *sedimentation rate*. If any of these functions is persistently elevated, one can be reasonably sure that the patient has either an infection or some other process such as neoplasm, thrombosis, infarction, arteritis, etc., which is causing tissue injury. (The procedures utilized in differentiating these various conditions are discussed in Chapter 33.) The presence of persistently normal values for these functions makes it unlikely that a bacterial infection exists at a sufficiently active level to cause weakness, but does not exclude parasitic and other infections which may produce weakness by causing anemia or by interfering with nutrition.

*The presence of a persistent tachycardia* (greater than can be accounted for by the level of the temperature) is suggestive of thyrotoxicosis, subacute rheumatic fever, or a psychogenic disorder. In the last condition, unlike the other two, the *sleeping pulse rate* is likely to be normal, and the hands, though moist, are usually cold.

*The decision as to whether anemia, from whatever cause, is of sufficient severity to cause weakness* can be made readily by measurement of the hemoglobin. When this substance is reduced from the normal level by more than one third, the patient is likely to complain of weakness. When its value is three fourths or more of the normal, it is unlikely that a complaint of weakness can be ascribed to anemia. Once anemia of significant degree has been demonstrated, the problem becomes that of determining its nature and cause (Chapter 22).

In deciding whether advanced nutritional deficiency is responsible for weakness, one can rely on objective methods; but *in the earlier*

*stages of the deficiency diseases the chief reliance has to be placed on the dietary history, supplemented, in certain instances, by saturation tests, etc. (Chapter 40).*

In the decision concerning the possible causative role of endocrine and metabolic factors, *the examination of the skin* (texture, warmth, moisture, distribution of hair, pigmentation, etc.), *the heart rate*, *the blood pressure*, *the palpable endocrine organs* (thyroid, ovaries, and testes), as well as *measurements of certain constituents of blood and urine* (sugar, sodium, iodine, cholesterol, calcium, phosphorus, phosphatase), plus certain special determinations (basal metabolic rate, glucose tolerance, eosinophil count, calcium balance, etc.), are of especial importance (Chapter 52).

*The story as regards habits* (alcohol), *occupation* (lead, etc.), and *drugs* offers the main clue for the diagnosis of exogenous intoxication as the cause of weakness.

*The social history* as regards the patient's happiness and problems in relation to home, work, and finances, is essential in the decision as to whether or not the weakness is of emotional origin.

The considerations which have been mentioned will lead to an accurate evaluation of the cause of weakness in many patients. Even so, there will remain a group of subjects (unfortunately, not rare) in whom the most exhaustive investigation fails to uncover the cause. In some such instances time will furnish the answer, but in others the patient will eventually recover entirely from his weakness while the cause remains obscure.

*To summarize:* The complaint of "weakness," as ordinarily employed by patients, is so vague as to be almost meaningless. Recurrent sudden weakness, which is closely allied to faintness and syncope, is discussed later. When the patient complains of persistent weakness, a sharp distinction must be drawn between lack of energy (lassitude), which is frequently due to emotional disturbances, and the loss of muscular strength (asthenia, debility), which may be due to serious disorders of metabolic or neuromuscular origin, or, more commonly, to senility or prolonged confinement to bed. Chronic infections and anemia are common causes of lassitude, but do not cause debility except when of severe degree. Nearly all

Table 4

IMPORTANT POINTS IN DIFFERENTIAL DIAGNOSIS OF SOME OF THE MORE COMMON CAUSES OF OBSCURE PERSISTENT WEAKNESS

<i>General Group of Causes</i>	<i>More Specific Causes</i>	<i>Commonly Associated Symptoms</i>	<i>Likely Physical Findings</i>	<i>Remarks</i>
Obscure chronic infection	Any chronic infection	Fatigue Anorexia Weight loss	Slight fever Tachycardia	Rapid sedimentation rate
	Tuberculosis	Weight loss and cough	Incipient: none Advanced: rales, etc.	X-ray, positive tuberculin test* Tubercle bacilli in sputum
	Chronic brucellosis	Fatigue	None	History of ingestion of raw milk Positive brucellergin test* Brucella agglutination, blood culture positive
	Subacute rheumatic fever	Weight loss, cough, and palpitation	Early signs of valvular disease Disproportionate tachycardia	History of joint pain, chorea, or epistaxis Response to salicylates Electrocardiogram
Anemia		Palpitation Fatigue Anorexia	Pallor	Reduction of hemoglobin, cell volume, etc.
Endocrine and metabolic disorders	Hypothyroidism	Coldness Drowsiness Loss of hair Slow speech Deep voice	Puffy facies Dry skin Delayed relaxation of tendon reflexes	Basal metabolic rate decreased Blood cholesterol increased
	Hyperthyroidism	Nervousness Palpitation Polyphagia Weight loss	Tachycardia Goiter; tremor Exophthalmos Warm, moist skin	Basal metabolic rate increased
	Diabetes	Polyphagia Weight loss Polyuria Polydipsia	None	Urine sugar Fasting blood sugar Glucose tolerance test
	Simmonds' disease	Extreme anorexia Loss of libido	Hypothermia Hypotension Smooth skin	Fasting hypoglycemia Flat glucose tolerance curve
Psychogenic disorders	Addison's disease	Nausea Vomiting Diarrhea	Hypotension Cutaneous and oral pigmentation	Low blood sodium (during crises) Water load (Kepler test) Eosinophil test
		Nervousness Insomnia Indigestion Palpitation	Hyperactive tendon reflexes Cold, moist hands Tachycardia	History of emotional disturbance, anxiety, worry, etc.

\* The presence of a positive skin test does not constitute adequate grounds for the assumption that tuberculosis or brucellosis is the cause of the symptoms.

patients with true asthenia have lassitude, but the majority of patients with lassitude do not have asthenia. A large percentage of the individuals who suffer from any physical or emotional disorder have lassitude, and the diagnosis is usually approached from the standpoint of the associated symptoms. When lassitude is the presenting complaint, one thinks first of an emotional disturbance, and then of chronic infections, anemia, and metabolic disorders. The exact chemical and physiologic mechanisms responsible for lassitude and asthenia are unknown, with the notable exception of myasthenia gravis.

### RECURRENT WEAKNESS AND SYNCOPE

Many patients complain of seizures of faintness, "dizziness" (which, when not associated with vertigo or a sense of rotation, usually means "lightheadedness"), of momentary decrease in alertness, or simply of "weak spells." Since these various sensations are not readily definable and shade into each other, and since a temporary loss of vigor and alertness is common to all of them, they may be considered together. Furthermore, in many instances the seizure may proceed to momentary loss of consciousness or syncope, and hence this symptom may likewise be logically considered in any discussion of recurrent weakness. As a general rule it may be stated that almost any disorder which (when of mild degree) produces momentary weakness may (when more severe) produce syncope.

Although much remains to be learned concerning the pathogenesis of this group of disorders, it is certain that some of the causes, and probable that most of them, induce faintness by leading to temporary disturbances in the metabolic processes in the brain. Such disorders may be divided into those in which the disturbance is clearly the result of diminished flow of blood, those in which the disorder results from a change in the composition of the blood, and those which are induced by primary disorders of the nervous system.

### THE MORE IMPORTANT CAUSES OF RECURRENT FAINTNESS AND SYNCOPE

- I. Temporary decline in cerebral blood flow:
  - A. Local: Cerebral vasospasm (hyperten-

sive encephalopathy). Temporary disturbances of motor or sensory function, often accompanied by loss of consciousness, commonly associated with an increased elevation of blood pressure in an already hypertensive subject

#### B. General:

##### 1. Cardiac:

- a. The several types of paroxysmal rapid heart action; instantaneous onset of tachycardia, with heart rates of 150 or more, lasting a few minutes to several days

##### b. Bradycardia:

- (1) Neurogenic (e.g., reflex bradycardia from carotid sinus)
- (2) Myogenic—heart block (Adams-Stokes syndrome)

- c. Mechanical hindrances to the heart (e.g., left atrial thrombus temporarily occluding mitral orifice; aortic stenosis)

##### 2. Peripheral:

- a. Psychogenic (due to sudden decline in blood pressure, resulting from emotional stimuli)

- b. Postural hypotension (decline in blood pressure in the standing position):

- (1) Venous pooling (varicose veins; deficient muscular tonus)

- (2) Inadequate postural vasoconstrictor reflex (disease of the spinal cord: prolonged bed rest)

#### II. Temporary disturbances of the composition of the blood:

- A. Hypoglycemia (attacks of faintness, either induced by insulin or occurring spontaneously two to four hours after meals)

#### B. Tetany and allied conditions:

1. Hypocalcemia
2. Carbon dioxide deficiency resulting from hyperventilation (hysterical hyperventilation)
3. Sodium chloride deficiency as the result of excessive sweating

#### III. Primary disorders of the nervous system:

- A. Epilepsy (idiopathic and Jacksonian)
- B. Hysterical fits

## DIFFERENTIAL DIAGNOSIS

The differentiation of the several conditions which commonly cause decline in cerebral blood flow is discussed in some detail in Chapter 14, and only a few of the especially pertinent points need to be mentioned here.

When faintness is related to diminished cerebral circulation caused by cardiac disorders, there is likely to be a combination of pallor and cyanosis, dyspnea is frequent, and the veins may be distended. When, on the other hand, the peripheral circulation is at fault, pallor is usually striking but is not accompanied by cyanosis or respiratory disturbance, and the veins are collapsed. When the primary disturbance lies in the cerebral circulation, the face is likely to be florid and the breathing slow and stertorous. When the patient is seen during the attack, a heart rate faster than 150 per minute speaks for an ectopic rhythm, while a striking bradycardia (rate less than 30) suggests the presence of complete heart block and an Adams-Stokes seizure. (In a patient with faintness or syncope attended by bradycardia, one has to distinguish between the neurogenic [reflex] and the myogenic [Adams-Stokes] types. Occasionally, electrocardiographic tracings will be needed, but as a rule the Adams-Stokes seizures can be recognized by their longer duration, by the greater constancy of the heart rate, by the presence of audible atrial sounds, and the marked variation in intensity of the first sound, despite the regular rhythm.)

The color of the skin, the character of the breathing, the appearance of the veins, and the rate of the heart are, therefore, valuable clues in diagnosis *if the patient is seen during an attack*. Unfortunately, the physician does not have the opportunity to see most of the patients during their "spells" of weakness. Hence he has to rely upon the patient's story in order to obtain the proper clue. It is, therefore, of primary importance that the physician be familiar with the *circumstances, the precipitating and alleviating factors* in regard to a given cause. These points are summarized in table 5, which deals only with those conditions which are fairly common, and in which the seizure of weakness or syncope is likely to be a dominant complaint.

Of the several factors in the story which may be helpful in arriving at a diagnosis, the following are often especially valuable:

**1. Type of Onset.** When the seizure begins instantaneously, a disturbance of the cardiac rhythm is probably at fault. When it sets in over a period of a few seconds, carotid sinus syncope or postural hypotension is likely. An aura at the onset suggests idiopathic epilepsy. When the symptoms develop gradually during a period of several minutes, hypoglycemia (spontaneous or induced by insulin) is to be considered. Onset of syncope during or immediately after exertion is common in patients with aortic stenosis and in elderly subjects with postural hypotension; exertional syncope is likewise occasionally seen in persons with aortic insufficiency.

**2. Position at Onset of Attack.** The position at the onset of the attack is of diagnostic import. Attacks due to hypoglycemia and hyperventilation, to cerebral vasospasm, or to change in cardiac rhythm are likely to be independent of posture. Seizures associated with a decline in blood pressure (including carotid sinus attacks) usually occur only in the sitting or standing position, while weakness resulting from orthostatic hypotension or orthostatic tachycardia is apt to set in immediately after the change from the recumbent to the sitting position.

**3. Associated Symptoms.** The associated symptoms during the seizure are important, for palpitation is likely to be present when the attack is due to disturbance in cardiac rhythm or to hypoglycemia; while numbness, a "drawing" feeling in the extremities, or irregular jerking movements without loss of consciousness are usual during attacks of hysterical hyperpnea. Genuine convulsions during the seizures are most common in epilepsy but occasionally occur in hysterical fits, hypoglycemia, and heart block.

**4. Duration of Seizure.** When the duration of the seizure is very brief, i.e., a few seconds to a few minutes, one thinks particularly of carotid sinus syncope, emotional syncope, the petit mal type of epilepsy, or one of the several forms of postural hypotension. A duration of more than a few minutes, but less than an hour, is particularly suggestive of hypoglycemia.

In many patients who complain of recurrent weakness or syncope but who do not have spontaneous seizures while under the observation of the physician, the most valuable method of diagnosis consists in an attempt to *reproduce* the attacks. Here, due allowance must be made for

Table 5

DIFFERENTIAL DIAGNOSIS OF SOME OF THE MORE COMMON CAUSES OF RECURRENT ATTACKS OF WEAKNESS OR SYNCOPE

Group	Disorder	Type of Onset	Position at Onset	Duration of Attack	Factors Affecting Attack		Important Findings During Attacks	Remarks
					Precipitating	Alleviating		
Intermittent bradycardia	Heart block	Sudden	Any	Seconds to hours	Unknown	Ephedrine*	Heart rate < 40	Enlarged heart Electrocardiogram
	Hypersensitive carotid sinus	Sudden	Sitting or standing	Seconds	Turning head Tight collar	Recumbent posture	Bradycardia Hypotension	Attack reproduced by pressure on carotid sinus
Intermittent tachycardia	Orthostatic	Sudden	Standing	Minutes	Standing	Recumbency	Tachycardia	on standing
	Paroxysmal ectopic tachycardia†	Instantaneous	Any	Minutes to days	See Chapter 235	See Chapter 235	Heart rate 150+	Electrocardiogram Palpitation
Temporary hypotension	Orthostatic	Sudden	Standing	Minutes	Standing	Recumbency	Marked decline in blood pressure on standing	
	Emotional syncope	Sudden	Standing	Seconds to minutes	Anxiety Fright Pain	Recumbency	Hypotension Bradycardia	Subjects usually healthy
Chemical disorders	Hypoglycemia	Gradual	Any	Minutes	Excessive starch intake Fatigue	Eating	Palpitation Anxiety Sweating Tremor	Usually begins 2-4 hours after meals
	Hysterical hyperpnea	Gradual	Any	Hours	Emotional upset	Rebreathing	Panting Tetany Numbness	No evidence of disease of heart or lungs
Etiology unknown	Idiopathic epilepsy	Sudden with aura	Any	Minutes to hours	Unknown	Sedatives	Deep coma Convulsions	Family history Electroencephalograms

\* Only when attacks are related to cardiac arrest. Diagnosis in the rare cases due to ventricular fibrillation requires ECG during attack.

† Including auricular fibrillation, auricular flutter, auricular tachycardia, and ventricular tachycardia (see Chapter 235).

the effects of suggestion, and rigid controls are necessary. Thus if one wishes to determine whether the seizures in a given subject are reproducible by insulin injection, and thereby to confirm a suspected diagnosis of spontaneous

hypoglycemia, it is necessary to control the observations by injecting other drugs such as atropine, nitroglycerin or histamine, which produce definite symptoms that are different from those caused by insulin. When properly

controlled, the insulin test is of great value in the diagnosis of spontaneous hypoglycemia. Without such controls the procedure is useless.

Among the other conditions in which the diagnosis is commonly clarified by reproducing the attacks are carotid sinus hypersensitivity (pressure on one or the other carotid sinus), orthostatic hypotension and orthostatic tachycardia (observations of pulse rate, blood pressure and symptoms in the recumbent and standing positions), and hysterical hyperpnea (determining whether the symptoms occur when the patient undertakes prolonged voluntary hyperventilation). In all such instances one should remember that *the crucial point is not whether symptoms are produced* (the procedures mentioned frequently induce symptoms in healthy persons), *but whether the exact pattern of symptoms which occur in the spontaneous attacks is reproduced in the artificial seizures.*

The most common type of syncope is the psychogenic (vasovagal, vasodepressor) type. However, the condition rarely offers difficulty in diagnosis because of the clear relationship to emotional stimuli, if one searches for them carefully.

Perhaps the most frequent cause of obscure recurrent attacks of weakness without syncope is spontaneous hypoglycemia. This condition, when severe, is likely to be dependent on a serious underlying cause such as a tumor of the islets of Langerhans, or advanced adrenal, pituitary, or hepatic disease; and in such instances, loss of consciousness is common. However, when mild, as is usually the case, hypoglycemia is commonly related to improper dietary habits, and can usually be diagnosed by the following criteria: The subjects usually ingest large quantities of carbohydrates and relatively little protein. The attacks are prone to occur two to five hours after the preceding meal, and do not occur within an hour after eating. During the seizures faintness, anxiety, sweating, giddiness, palpitation, choking sensations, and vague precordial discomfort are common. The symptoms during the seizure are not strikingly relieved by the recumbent position, and this feature may be of value in differentiation from the conditions dependent on diminished cerebral blood flow. The attacks can be alleviated by the ingestion of orange juice or other carbohydrate-containing

foods. The fasting blood sugar is often normal, but the values attained three hours after the ingestion of glucose are usually either somewhat subnormal or within the lower limits of the normal range. The seizures can be reproduced by the injection of insulin, and can usually be prevented by the use of a diet which is low in carbohydrate and high in protein, administered in small, frequent feedings. This disorder is very common, and is frequently misdiagnosed either as "organic heart disease" or as "neurosis."

Other common and frequently overlooked causes of recurrent weakness are carotid sinus hypersensitivity and postural hypotension. The former condition is diagnosed by reproduction of the symptoms through pressure on the appropriate area. It should be recognized that the sensitivity to carotid sinus pressure bears a relation to circumstances: position, blood sugar level, and drugs affecting vagal tone.

Postural hypotension is of two general types, one of them occurring in the presence of organic disease of the nervous system (and especially that associated with diabetes and tabes dorsalis), while the other occurs in elderly subjects (usually males) who have lost weight and whose muscles have become flabby through lack of exercise. The story of weakness or syncope coming on immediately after change from the recumbent to the standing position usually furnishes the initial lead, and the diagnosis is confirmed by measurements of blood pressure in the two positions, and also by prevention of the symptoms by various methods of treatment (abdominal binders, vasoconstrictor drugs, sleeping with the head of the bed elevated) which tend to prevent the decline in blood pressure in the upright position.

Epilepsy, whether of the idiopathic or the Jacksonian (focal) variety, is one of the most common causes of repeated loss of consciousness. Because of its frequency, epilepsy is often erroneously considered to be the cause of syncopal attacks brought on by one of the conditions previously mentioned. The history of onset in childhood or during adolescence, the presence of the characteristic aura prior to the seizure, and the lack of evidence for the presence of circulatory or chemical disorders capable of causing syncope, plus the presence of the characteristic electroencephalographic pattern, will usually point the way to the diagnosis, provided it

is remembered that some patients with the milder forms may have seizures lasting only a few seconds.

*To recapitulate:* Recurrent weakness and recurrent syncope have been discussed together because they are likely to be produced by the same conditions. The most common causes of these conditions are idiopathic epilepsy, emotional disturbances, spontaneous hypoglycemia, postural hypotension, carotid sinus hypersensitivity, and temporary disturbances of the cardiac rhythm. Since the attacks are of brief duration, the patients are not likely to be seen during the spontaneous seizures. The diagnosis, therefore, depends in large measure on a carefully taken history concerning the exact circumstances surrounding the attacks, and on the ability of the physician to reproduce the seizures, once the true cause is suspected.

In conclusion, it should be emphasized that the majority of conditions which produce recurrent weakness are not dangerous. The attacks are likely to be interpreted by the patient, and occasionally by the physician, as being due to serious disease of the circulatory apparatus or of the nervous system. Hence, most of the patients suffer from anxiety which is out of all proportion to the seriousness of the condition. When the mystery has been solved by careful study, and by production of the attacks, the condition is usually at least moderately amenable to treatment, and when its exact significance has been explained to the patient his fears are usually alleviated. Here, as elsewhere in medicine, a careful analysis of symptoms, when coupled with a clear understanding of their mechanism, enables the physician to have a happier as well as a healthier patient.

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# 8

## Coma, Convulsions, and Paralysis

T. R. Harrison, H. Houston Merritt, and Daniel Sciarra

### Coma

Classification of Common Causes of Coma  
Coma Due to Chemical Disturbances of Brain  
Coma Due to Physical Disturbances of Brain  
Diagnostic Procedure in a Comatose Patient

### Convulsions

Mechanism  
Differential Diagnosis  
Procedure with Patients Suffering Seizures

### Paralysis

Monoplegia  
Hemiplegia  
Paraplegia  
Quadriplegia  
Isolated Paralysis

## COMA

T. R. Harrison

Unconsciousness, like weakness, may be either recurrent or persistent. The causes of recurrent unconsciousness, or syncope, have been considered in the previous chapter. Here, we are concerned only with persistent unconsciousness or coma. This phenomenon may be defined as a state of prolonged unconsciousness from which the subject cannot be aroused. It is commonly preceded by *stupor*, which is a state of diminished acuity of consciousness from which the subject can be aroused, and it may alternate with *delirium*, in which consciousness is disordered rather than lost. The distinction between coma and syncope is relative rather than absolute, for it depends on the duration of the unconscious state. For practical purposes it is perhaps wise to consider unconsciousness lasting for hours or longer as coma, while loss of consciousness for a few minutes only should be classified as syncope. As compared to syncope, coma usually develops less rapidly, is less apt to be recurrent, and is much more likely to lead to a fatal outcome.

Although the exact mechanisms responsible for coma are, for the most part, unknown, they may be conveniently divided into two groups, according to whether the disturbance in the brain is primarily of chemical or of physical nature.

### CLASSIFICATION OF COMMON CAUSES OF COMA

#### I. Chemical Disturbances:

A. Deficiencies (of oxygen, glucose, or vita-

mins) (See preceding chapter, section on Syncope)

#### B. Excesses (Intoxications—Chapter 92):

1. Exogenous (especially alcohol, opiates, barbiturates, bromide, and carbon monoxide)
2. Endogenous (diabetic, uremic, and hepatic)

#### II. Physical Disturbances:

##### A. Temperature:

1. Hypothermia (rarely primary; usually secondary to alcohol, barbiturates, or circulatory failure)
2. Hyperthermia (severe infections, lesions of the hypothalamus, and heat stroke)

##### B. Pressure:

1. Neoplastic
2. Inflammatory (meningitis, encephalitis, abscess)

##### C. Circulatory:

1. Vasospasm (hypertensive encephalopathy)
2. Thrombosis
3. Embolism
4. Hemorrhage:
  - a. Cerebral
  - b. Subarachnoid

##### D. Traumatic:

1. Concussion (with or without fracture)
2. Subdural hematoma (acute or chronic)
3. Epidural hematoma

Since the chemical and physical disturbances naturally may overlap, their separation is relative rather than absolute. The chemical disturbances usually produce no localizing neurologic signs, although bilateral Babinski's sign may occur occasionally; the physical disturbances frequently are associated with such phenomena, which are often more marked on one side of the body than the other. Many of the physical disturbances of the brain tend to produce convulsions; these occur less commonly as the result of a chemical disturbance, although they are sometimes observed during uremic and hypoglycemic

coma, and may even be a feature in the rarer types of intoxication.

### COMA DUE TO CHEMICAL DISTURBANCES OF THE BRAIN

These disturbances may be the result of *deficiencies* or of excesses (*intoxications*). The most important deficiencies are those of oxygen or of glucose (both of which at times may produce prolonged coma, but which have been considered in the preceding chapter because they are more likely to be associated with recurrent weakness or syncope than with actual coma); of water, which will be discussed in Chapter 28; and of certain vitamins, such as nicotinic acid, the lack of which may be accompanied by coma in patients with advanced pellagra. The coma of pellagra usually may be recognized readily by the associated changes in the skin and mouth, as well as the coexisting diarrhea and the dietary history (Chapter 44).

The *intoxicants* which lead to coma may be *exogenous* or *endogenous*. Of the exogenous group, *alcohol* is the most important; coma due to this substance is recognized by the history, the odor of the breath, and the hyperemia of the face and mucous membranes. One should remember, however, that alcoholic sprees frequently lead to falls, quarrels, and other causes of head injuries; furthermore, that the use of alcohol often leads to the concomitant use of various sedative drugs; and, finally, that acute alcoholism may precipitate diabetic coma or cerebral hemorrhage in predisposed subjects. Hence the presence of an *alcoholic* breath should not lead one to the conclusion that the coma is due solely to alcohol until other possible causes have been eliminated. Pronounced hypoglycemia does not usually occur in patients with alcoholic coma unless the "spree" has been of unusually long duration, or unless methyl alcohol has been ingested.

Of the various sedative drugs which may produce coma, the barbiturates, bromides, and opiates are the most important. The combination of symmetrically contracted pupils and diminished respiratory rate should immediately lead to the suspicion of morphine *alkaloid intoxication*. Unexplained coma in any patient (and especially if the body temperature be subnormal) should cause one to suspect *barbiturate intoxication* (frequently as the result of attempted suicide), and the urine should be analyzed for barbiturate con-

tent. When, on the other hand, the coma is attended by delirium, and there is a history that some type of drug (usually a "patent medicine") has been ingested for several weeks, *bromide intoxication* is probable, and analysis of the blood for bromide content is indicated.

Carbon monoxide poisoning may produce prolonged coma which is usually associated with "cherry red" discoloration of the lips. When exposure has been prolonged, the coma may persist, as the result of damage to the brain, after the restoration of oxyhemoglobin and the disappearance of the "cherry red" discoloration. The coma due to methemoglobinemia induced by nitrates, chlorates, and other substances is attended with intense cyanosis, and the blood has a chocolate brown color.

Of the endogenous intoxications, diabetic, uremic, and hepatic coma constitute the classic examples. In each of these conditions "dehydration" and acidosis may be important factors, but, in addition, there are certain toxic metabolites which probably play a dominant role in inducing the unconsciousness. The acetone bodies (acetooacetic acid, beta-hydroxybutyric acid, and acetone) are of first importance in diabetic coma, while it is probable that accumulation in the body of the phenolic derivatives of the aromatic amino acids, as the result of impairment of conjugation or of excretion, is partially responsible for the coma occurring in the terminal phases of hepatic and renal disease. Hypoglycemia is another important factor in inducing hepatic coma, while hypertensive encephalopathy, with attendant cerebral edema and vasospasm, is commonly present in uremic subjects.

The deep, sighing respiration (Kussmaul breathing, "air hunger"), the "spoiled fruit" odor of the breath, the soft eyeballs, the presence of hypotension, and other signs of extracellular fluid deficit (Chapter 28), are usually sufficient to raise the question of diabetic coma, and the diagnosis is readily established by appropriate analyses of blood and urine. The combination of hypertension (in spite of well-marked dehydration) with vascular retinitis and papilledema, plus the yellowish brown discoloration of the exposed parts of the skin, the generalized pallor of skin and mucous membranes, and the frequent occurrence of muscular twitchings, points toward uremia, but requires confirmation by investigation of the urine for protein and for fixation of

specific gravity, and especially of the blood for its contents of nonprotein nitrogenous substances. The presence of jaundice, of ascites, of an abnormally small or large liver, or of any combination of these findings in a comatose patient, points toward hepatic insufficiency—a condition which is likely to be particularly confusing when, as is occasionally the case, jaundice is absent.

### COMA DUE TO PHYSICAL DISTURBANCES OF THE BRAIN

**Disturbances in Temperature.** A change in body temperature in either direction may, when extreme, produce coma. Hypothermia, when occurring in an unconscious patient, is usually secondary to the action of the agent which causes the coma (e.g., alcohol or barbiturates). However, primary hypothermia such as results from excessive chilling of the body tends, *per se*, to induce coma. Hyperthermia likewise may be secondary to conditions (such as cerebral hemorrhage or tumors of the midbrain) which induce coma; or may be the primary cause of coma, as in the hyperpyrexia which occurs with heat stroke and sometimes with typhoid, typhus, pneumonia, malaria, and many other severe infections. As a general rule (to which typhoid fever is a frequent exception), the prognosis is poor in a patient presenting the combination of coma and marked elevation of body temperature.

**Disturbances in Pressure.** Regardless of cause, increased intracranial pressure of severe degree leads to coma, which is related to the interference with cerebral blood flow induced by the rise in pressure in the rigid cranial cavity, and frequently also to the focal cerebral disturbances caused by the responsible lesion. The rather numerous conditions which may cause a rise in intracranial pressure may be divided conveniently into neoplastic, inflammatory, and circulatory types.

*Neoplasm* of the brain should be suspected in any patient presenting a steadily progressive neurologic disorder, accompanied by signs of a focal lesion. The inflammatory conditions causing increased intracranial pressure may be divided into *meningitis* (characterized by fever, stiffness of the neck, retraction of the head, positive Kernig's sign, and well-marked increase in the content of cells and protein in the cerebrospinal fluid); *encephalitis* (characterized by simi-

lar but less striking findings in proportion to the depth of the coma); and cerebral *abscess*, cerebral *malaria*, and cerebral *thrombophlebitis*.

Coma due to disturbances in cerebral circulation may or may not be accompanied by increased intracranial pressure. In *cerebral embolism* and *thrombosis* this function usually remains within normal limits. Contrariwise, the intracranial pressure is commonly elevated as the result of cerebral edema during the attacks of *hypertensive encephalopathy* (Chapter 243) which occur in patients with eclampsia, glomerulonephritis, malignant nephrosclerosis, and, rarely, benign nephrosclerosis. *Intracranial hemorrhage*, likewise, usually results in increased intracranial pressure. The most common type of cerebral hemorrhage occurs in the region of the internal capsule, and produces paralysis of one half of the body. *Subarachnoid hemorrhage*, which is less frequent, is characterized by severe headache, fever, signs of meningeal irritation, and grossly bloody cerebrospinal fluid.

Either acute heart failure or, more commonly, peripheral circulatory failure (Chapter 14) may, when sufficiently severe, precipitate coma.

**Disturbances Resulting from External Violence.** These are of several types. The direct effects of trauma are *concussion* and *fracture*, and in both instances the comatose state tends to occur immediately after the injury. An indirect effect may be compression of the brain as the result of acute or chronic *subdural hematoma*, and in such instances a latent period (the "lucid interval") of minutes, hours, or longer, supervenes between the injury and the onset of coma. When the lucid interval is very short, and quickly followed by coma and other signs of increased subcranial pressure, it should be suspected that the hemorrhage is of arterial origin (usually from the middle meningeal artery), and proper surgical procedures should be instituted immediately.

Since the mechanism of epilepsy is not definitely known, the *coma which follows epileptic seizures* cannot be classified readily. The history of previous attacks and of convulsions at the onset, as well as evidence that the tongue has recently been bitten, or that there has been fecal or urinary incontinence during the seizures, should lead to the suspicion that this type of coma is present. Electroencephalograms may be

of great diagnostic value in patients observed between the suspected epileptic seizures.

### DIAGNOSTIC PROCEDURE IN A COMATOSE PATIENT

Before attempting to arrive at a conclusion as to the cause of coma, one should take cognizance of certain simple therapeutic principles, including the necessity for traction on the tongue to prevent suffocation, the desirability of emptying the oral cavity by suction, and the possible danger of manipulation of patients who, having been severely traumatized, may be suffering from an unrecognized vertebral injury.

Since unconscious patients are likely to be seriously ill and may require immediate treatment, the usual detailed history is postponed and the initial history should be taken quickly, with emphasis on the type of onset, including inquiry as to injury and drugs, and also inquiry concerning preexisting illness such as diabetes or epilepsy.

In order that such information may be obtained, it is important that persons bringing a comatose patient to a hospital not be allowed to leave before they can be questioned.

Observations concerning the reaction to painful stimuli may be helpful in determining the depth of coma, and the presence or absence of paralysis. A careful search for signs of trauma to the head should be made. The breath is then smelled in order to detect alcohol, the "spoiled fruit" odor of diabetic coma, or the uriniferous odor which is frequent in uremic subjects. One looks next for evidence of paralysis. (The cheek on the paralyzed side tends to "balloon" out during expiration, the face is drawn toward the normal side, and the extremities on the affected side lack muscle tone in the early stages, but later become stiff.)

The body temperature is then taken, a well-marked elevation suggesting either a severe systemic infection such as pneumonia, an intracranial infection such as meningitis, or a focal cerebral lesion such as hemorrhage or tumor which is affecting the heat-regulating center of the midbrain. An excessively high body temperature ( $107^{\circ}$  to  $110^{\circ}$  F.), associated with dry skin, should arouse the suspicion of heat stroke. Pronounced hypothermia is especially suggestive

of alcohol, barbiturate, or peripheral circulatory failure (Chapter 14) as the cause of coma.

The character of the respiration is noted. Slow breathing points toward morphine intoxication, or toward a lesion causing increased intracranial pressure, in which case the respiration is likely to be stertorous also; while deep breathing with moderate increase in rate suggests diabetic coma.

The pulse rate is of little value in the differential diagnosis of coma, unless it be either exceptionally slow or excessively rapid (above 160 per minute), in which case there is the possibility that unconsciousness has been precipitated by an ectopic rhythm. Bradycardia of moderate degree is common in patients with acute increase in intracranial pressure, and marked bradycardia in a comatose patient suggests heart block (Adams-Stokes seizure).

Measurement of the blood pressure may furnish an important clue to the cause of the coma. Marked hypertension is common in subjects with cerebral hemorrhage, hypertensive encephalopathy, and uremia; while pronounced hypotension suggests that the unconsciousness may be due to diabetes, alcohol, barbiturates, or internal hemorrhage.

Inspection of the skin is of special importance in regard to signs of trauma. Hyperemia of the face suggests alcohol as a possible cause of coma, while marked pallor leads to the suspicion of internal hemorrhage. The presence of a maculo-hemorrhagic rash speaks for typhus, Rocky Mountain spotted fever, or meningococcal infection. The latter disorder and, less commonly, other acute infections, may lead to profound and rapidly fatal coma when complicated by acute adrenal necrosis, or by massive hemorrhage into the adrenal glands (Waterhouse-Friderichsen syndrome, Chapter 103).

An attempt is made to elicit Kernig's sign (inability to extend the leg at the knee joint when the thigh is flexed at the hip), and to flex the head on the chest. If the head cannot be so flexed and Kernig's sign is positive, it is likely that the patient has either meningitis or subarachnoid hemorrhage. The pupils are then inspected. Unilateral dilatation suggests a focal intracranial lesion; bilateral dilatation of moderate degree is common but not constant in barbiturate intoxication; symmetric constriction ("pinpoint") points toward opiate intoxication. Ophthalmoscopic examination is then performed. Edema of

Table 6

IMPORTANT POINTS IN THE DIFFERENTIAL DIAGNOSIS OF SOME OF THE MORE COMMON CAUSES OF COMA

General Group	Subgroup	Specific Disorder	Important Clinical Findings	Important Laboratory Findings	Remarks
Chemical disorders	Exogenous intoxication	Alcohol intoxication	Hypothermia, hypotension, flushed skin, alcohol breath	Elevated blood alcohol	
		Barbiturate intoxication	Hypothermia, hypotension	Barbiturates in urine	
		Opium intoxication	Slow respiration, cyanosis, constricted pupils		History of intake of intoxicating substance
		Bromide intoxication	Hyperthermia, delirium	Blood bromides ++	
		Carbon monoxide intoxication	Cherry red skin	Carboxyhemoglobin	
	Endogenous intoxication	Diabetic coma	Signs of extracellular fluid deficit, deep respiration, "fruity" breath	Glycosuria, hyperglycemia, reduced CO <sub>2</sub>	Acetone bodies in urine
		Uremia	Hypertension, yellowish brown skin, uriniferous breath	Proteinuria, blood urea ++	Vascular retinopathy
	Increased intracranial pressure	Meningitis	Stiff neck, positive Kernig, fever	Changes in spinal fluid	
		Brain tumor	Stertorous breathing, neurologic signs dependent on location, papilledema		Steady progression of signs and symptoms
Physical disorders	Cerebral circulatory disturbances	Cerebral hemorrhage	Stertorous breathing, hypertension, flushed skin, hemiplegia		Sudden onset, elderly subjects
		Subarachnoid hemorrhage	Fever, stertorous breathing, hypertension, stiff neck, positive Kernig	Bloody spinal fluid	Sudden onset, after headache
		Cerebral thrombosis	Paralysis of relatively slow onset		Senile patients
		Cerebral embolism	Sudden onset of paralysis		Evidence of heart disease
		Cerebral vasospasm	Hypertension, flushed skin, any focal neurologic signs		Brief duration: few minutes to few days
	Trauma	Fracture or concussion	Signs of skin trauma	Skull fracture in x-ray	Bleeding from nose or ears, history of trauma
		Subdural hematoma	Slow respiration, rising blood pressure	Increased spinal fluid pressure	History of trauma
	Hyperpyrexia		Extreme hyperthermia, rapid respiration	Dependent on causes	Evidence of a specific infection, of heat stroke, or intracranial disease
Miscellaneous		Idiopathic epilepsy		Characteristic electroencephalogram	History of previous attacks
		Hysteria	Respiration often rapid, bizarre behavior		"Barbiturate interview"

the optic nerve head, a sign of increased intracranial pressure and vascular retinopathy (scattered patches of hemorrhage and exudate), is an indication of the advanced hypertensive vascular disease which often accompanies uremia, cerebral hemorrhage, or hypertensive encephalopathy.

Examination of the urine is of specific diagnostic value in patients with coma induced by barbiturates, and is of great importance in the recognition of diabetic and renal coma. However, one should remember that proteinuria may result not only from renal disease but also from convulsions or fever; that glycosuria is not an invariable sign of diabetes but may also occur in patients with cerebral lesions or meningitis, and in those with myocardial infarction; and that acetonuria may result from prolonged starvation or from vomiting as well as from diabetes.

The most important examinations of the blood in comatose patients are those for urea (or total nonprotein nitrogen), sugar, carbon dioxide-combining power, and bromide. In general, the decision as to which of those substances should be measured will depend on the clinical picture, but in case of doubt all should be determined.

Spinal puncture is often a valuable procedure and should be employed in all cases of unexplained coma, but should always be preceded by examination of the retinas, and should be undertaken with great caution when there is a reasonable possibility of an intracranial space-occupying lesion such as a tumor or abscess. If doubt exists on the point, the procedure should be postponed or done with great caution, only enough spinal fluid being removed, at a slow rate, to allow measurement of pressure (in a small-bore manometer), and for cell count. Otherwise, the increased pressure may force the medulla into the foramen magnum and cause death. In a comatose subject the spinal fluid examination is of particular diagnostic value under the following circumstances: (1) in proving that there is increased intracranial pressure; (2) in demonstrating bleeding (traumatic or spontaneous) into the subarachnoid space; (3) in differentiating the various processes which cause meningeal irritation—i.e., in separating the several types of meningitis from each other, and from subarachnoid hemorrhage and meningismus.

When a suspicion of trauma exists, roentgenograms should be made in a search for fracture of the skull, which exists in a goodly percentage of

the cases. When, however, it is certain that trauma is responsible for the coma, it will usually be wise to defer roentgenographic examination until the necessary immediate therapeutic measures have been instituted.

The more important points in the differential diagnosis of the commoner causes of coma are summarized in table 6.

Further discussions concerning the differential diagnosis of the disorders which may cause coma will be found in the several chapters dealing with the various specific diseases which have been mentioned. The purpose of this section has not been to consider the subject of coma in detail, but rather to outline the underlying mechanisms, and to indicate some of the general principles which are of value in distinguishing between the more common causes of this important clinical phenomenon.

## CONVULSIONS

H. Houston Merritt and Daniel Sciarra

Most of the conditions already discussed, which are capable of inducing coma, may at times cause convulsions. The discussion to follow will be centered on those primary disorders of the nervous system in which coma is likely to be only incidental to convulsions rather than on the various systemic disorders already considered, in which convulsions are likely to be incidental to coma. The discussion will deal, in the main, with the causes of recurrent convulsions. The unqualified term "epilepsy" will be used to designate recurrent convulsions regardless of cause, and the term "idiopathic epilepsy" to denote the specific symptom complex of recurrent convulsions of unknown etiology beginning in early life.

## MECHANISM

Convulsive seizures are associated with many varied and different disease processes. Some of these are focal cerebral lesions. Others, however, are generalized physiologic disturbances associated with organic disease in the nervous system, or elsewhere in the body. The great diversity of conditions with which convulsive seizures may be associated has led to a search for a mechanism which could serve as a common denominator. No single mechanism can be postulated, though several do influence epileptic at-

tacks. Among these are the following: oxygen supply; acid-base equilibrium; change in blood calcium, glucose, or chloride; fluid balance; tissue permeability; and intracranial pressure (table 7).

Table 7

## FACTORS INFLUENCING EPILEPTIC ATTACKS

Factor	To Precipitate Seizure
Oxygen.....	Decreased
Acid-base balance.....	Alkalosis
Blood calcium.....	Decreased
Blood chloride.....	Increased
Fluid balance.....	Edema
Tissue permeability.....	Increased
Intracranial pressure.....	Increased
Glucose.....	Decreased
Acetylcholine.....	Increased
Acetylcholine esterase.....	Decreased

Decreased oxygen supply to brain tissue is the most prominent and constant factor in precipitating seizures, and perhaps tissue anoxia may be basic to all the other factors.

Disturbance of the acid-base equilibrium so as to induce alkalosis tends to precipitate seizures. However, there is an intimate connection between oxygenation and the acid-base balance. Alkalosis makes less oxygen available from hemoglobin, and thus oxygen deprivation may again be the prime factor. So also may the other factors operate to produce decrease of oxygen and thus to facilitate seizures.

In recent years attempts have been made to show that a disturbance in the regulation of acetylcholine is important in the mechanism of seizure production. Acetylcholine is a normal constituent of nervous tissue, and plays an important role in the transmission of the nerve impulse. It has been demonstrated that the application of acetylcholine-like compounds to the cerebral cortex results in the production of abnormal cortical discharges. It is also known that the injection of acetylcholine, intravenously or intracisternally, will result in the occurrence of seizures. Recent animal experiments with diisopropylfluorophosphate, which irreversibly inhibits the action of cholinesterase, as well as clinical experience with this compound, indicate that it can produce epileptiform cortical changes. The changes in the electroencephalogram produced by this drug are attributed to an accumulation

of excess of acetylcholine. Some confirmation of this hypothesis is afforded by the studies of other workers, who found an excess of acetylcholine in the cerebrospinal fluid of patients with seizures, especially in the period immediately following a seizure.

Thus many disease states may operate through one or several factors to precipitate a seizure. Some attempts have been made to trace the mechanism still further. The clinical phenomena of a fit are generally accepted as evidence of an abnormal nerve discharge. There has been argument as to whether the clinical phenomena of a convulsion are due to an actual stimulation of cortical nerve cells or whether they are due, in part at least, to a release of lower structures from control of higher centers.

Some observers consider the unconsciousness of an attack as a manifestation of cerebral inhibition, and the movements as evidence of release from higher centers. Other investigators consider the seizure to be a result of stimulation of higher centers. The best argument for this latter view is the striking resemblance of a clinical seizure to that obtained by faradic stimulation of the cortex.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis in patients with seizures may be approached in several ways.

The most common approach is to divide cases into symptomatic and idiopathic epilepsy or those with and those without demonstrable lesions in the nervous system or elsewhere in the body. This division serves to focus attention on discovering the lesion that is precipitating the attacks. Though this approach is of great clinical importance, it may lead to erroneous pathologic and physiologic concepts. The lesion in patients with so-called symptomatic epilepsy does not directly cause the seizure. On the other hand, the absence of demonstrable lesions in patients labeled as idiopathic epileptics may mean only that our limited methods of investigation fail to show them.

Another common method of dividing cases of epilepsy is based on the clinical manifestations present during the seizure. This method is of greatest importance in the medical treatment of patients with seizures. This approach to epilepsy divides the cases into three groups, which are not mutually exclusive. The three types of attacks

are: (1) grand mal (including generalized seizures with a focal or Jacksonian onset); (2) petit mal; and (3) psychomotor attacks.

Grand mal seizures are the classic examples of what is usually implied by a convulsion, though not all grand mal attacks conform to a distinctive pattern. They may vary in duration, in severity, and in their clinical manifestations. Characteristically, the seizures begin with a warning or aura, and are followed by precipitate loss of consciousness and tonic-clonic muscular spasms. Urinary and fecal incontinence may accompany the picture. Following the seizure the patient is often drowsy and tired, and may fall into a deep sleep. Jacksonian or focal seizures, without loss of consciousness, also can be classed as fragments of the grand mal picture.

Petit mal attacks occur most frequently in childhood and often disappear in puberty. They are manifested by a transient loss of awareness or clouding of consciousness, lasting for a few seconds and at times accompanied by slight movements of the head, eyes, or extremities. The patient feels perfectly well before and is mentally clear immediately after the attack. Other manifestations of petit mal include myoclonic jerks, great frequency of attacks (up to a hundred or more daily), and a typical electroencephalographic pattern.

Psychomotor or psychic equivalent seizures include a heterogeneous group of attacks that do not fit into the classic grand mal or petit mal pattern. Psychomotor attacks may be ushered in by an aura. They consist of periods of mental clouding lasting a few minutes or more, with the performance of automatic activities such as smacking the lips, removing clothes, aimless walking, or purposeless movements of the hands. After a mild attack the patient is confused or in a clouded state for a minute or more. In severe attacks the clouded mental state may last several hours, and the patient may perform acts of which he is unaware. Psychomotor attacks can thus be distinguished from petit mal mainly by the wider range of muscular movements and the longer duration of the attack. They are distinguished from grand mal attacks by the fact that the patient does not fall to the ground in an unconscious state with tonic-clonic movement.

Still another approach to division of the epilepsies is available. This stresses the classification of seizures based on the site of origin of the

epileptic discharge in the brain (table 8). Such a method is of special importance to neurosurgeons, since it focuses attention on location of possible lesions.

*Table 8*  
CLASSIFICATION OF SEIZURES\*

Clinical Type	Localization
SOMATIC MOTOR	
Generalized (grand mal)	Complete motor
Jacksonian (local motor)	Pre-Rolandic gyrus
Masticatory	Lower Rolandic
Simple adversive	Frontal
Tonic postural (decerebrate, opisthotonics)	Brain stem
SOMATIC SENSORY (AURAS)	
Somatosensory	Post-Rolandic
Visual	Occipital
Auditory	Temporal
Vertiginous	Temporal
Olfactory	Infratemporal
VISCELAR	
Autonomic	Diencephalic
PSYCHIC	
Dreamy state	Temporal
Petit mal	
Automatism (ictal and post-ictal)	
Psychotic states (secondary)	

\* Modified from Penfield and Erickson.

In the differential diagnosis in an individual case of epilepsy, a consideration of all three methods of approach may be necessary in distinguishing among the different diseases that may cause, accompany, or precipitate convulsions.

**1. Cerebral Disease.** Of all the morbid affections of the body, cerebral disease is by far the most common condition associated with symptomatic epilepsy. Almost any type of cerebral lesion may be found in conjunction with seizures. On the other hand, there is no type of cerebral lesion which is accompanied by seizures in 100 per cent of the cases. Seizures which occur in patients with cerebral lesions are usually of the grand mal type, less commonly of the psychomotor, and only rarely of the petit mal type.

**CEREBRAL TUMORS.** Seizures are a common accompaniment of brain tumors, occurring in 35 to 60 per cent of the cases with tumors in the cerebral hemisphere, and may be present as the initial symptom in about 12 per cent of cases. They are uncommon in patients with tumors in the brain stem or cerebellum.

**CEREBRAL TRAUMA.** Convulsions are uncommon as an immediate sequel of head injury. The frequency of the development of seizures in the months following an injury to the head is proportional to the severity of the brain damage. They occur in less than 0.5 per cent of patients with simple concussion, but the percentage of incidence increases to 40 or more per cent in the patients with penetrating wounds of the scalp, with fracture of the skull, and with laceration of the dura and cortex. The seizures may make their appearance at any time after the injury but, more commonly, the first seizures occur in the period between six months and two years after the trauma.

**CEREBRAL VASCULAR DISEASE.** Despite the great frequency of cerebral vascular accidents in the middle and older age groups, there is no great increase of incidence of seizures in this age group. Convulsive seizures are rare at the onset or as a sequel of simple arteriosclerotic thrombotic lesions. They occur at the onset in about 10 per cent of the patients with intracerebral hemorrhage. Convulsive seizures are a common sequel of vascular lesions in childhood or infancy. It is not known whether these lesions are chiefly arterial or venous in nature. Vascular malformations and tumors are accompanied by a high incidence of seizures, perhaps because they act as tumor masses.

**CEREBRAL INFECTION.** Seizures are not uncommon in all forms of infections of the cerebrum. Brain abscess is accompanied by seizures in about 50 per cent of cases, and they are apt to occur after the abscess has been removed surgically. The seizures that may accompany dementia paralytica, other forms of neurosyphilis, and other inflammatory diseases of the brain are in part related to focal cerebral lesions following thrombosis of smaller arteries or veins.

**DEGENERATIVE DISEASES.** The occurrence of fits in degenerative diseases is quite variable. Any type of degenerative disease may involve seizures; some types are very frequently so accompanied. Tuberous sclerosis is almost constantly associated with seizures. Convulsions occur but are relatively infrequent in patients with diffuse sclerosis, Alzheimer's disease, and Pick's cortical atrophy. Seizures occur in approximately 5 per cent of the cases of multiple sclerosis. They are rare in simple cerebral arteriosclerosis.

**CONGENITAL MALDEVELOPMENT.** Convulsions may be found in the schizencephalies and the forms of cerebral malformation which produce the common cerebral spastic paraplegias. Because of the development of seizures soon after birth, the etiology may be difficult to ascertain, for convulsions due to birth trauma may also manifest themselves in the immediate postnatal period.

**2. Physiologic Disturbance.** Conditions which disturb the body physiology may precipitate seizures by a concomitant disturbance in cerebral physiology. These conditions may be very diverse, may be located well out of the central nervous system, and yet may lead to convulsions, usually by a change in the fluid balance or oxygenation of the brain.

**ANOXIA.** The more direct causes of cerebral anoxia include suffocation, anesthesia, and carbon monoxide poisoning.

**CEREBRAL EDEMA.** Many conditions lead to seizures by increasing the fluid content of the brain. Cerebral edema is probably the mechanism of the production of convulsions in uremia, acute alcoholism, eclampsia, and some febrile illnesses.

**HYPOCALCEMIA.** Low blood calcium is associated with tetany, and excessively low levels of calcium in the blood may lead to seizures. Some of the causes of low blood calcium are hypoparathyroidism, infantile tetany associated with rickets, osteomalacia, sprue, celiac disease, pregnancy, lactation, and prolonged vomiting. Regardless of the cause, a sufficient drop in ionizable blood calcium will lead to convulsions.

**INTRACRANIAL PRESSURE INCREASE.** A rise in the intracranial pressure may be associated with convulsions. The mechanism here, however, is probably through cerebral edema and anoxia.

**HYPOGLYCEMIA.** Pancreatic tumors and overdosage of insulin will produce a drop in the blood sugar level. In the brain this probably accomplishes the same end as cerebral anoxia, and thus seizures may occur. Convulsions following attacks of so-called spontaneous hypoglycemia are possible, though rare. A history of seizures occurring hours after a meal, or following a period of fasting, is suggestive of such a condition. It is important that hypoglycemia acting as a precipitating factor in setting off convulsions due to some other disease process be differentiated from hypoglycemia as a primary cause of

convulsions. In the latter instance, but not in the former, the fasting blood sugar will usually be subnormal. (See Chapter 7.)

**CAROTID SINUS HYPERIRRITABILITY.** Stimulation of the carotid sinus will often lead to changes in a patient's pulse, or drop in blood pressure. Occasionally, however, the patient with a hyperirritable carotid sinus will have convulsions following sinus stimulation.

**3. Intoxications.** Among the more important poisons which produce convulsions are lead, strychnine, and tetanus toxin (Chapter 92). The two latter conditions should be suspected when the convulsions are of the spinal type (i.e., are tonic in character) and are induced readily by minor stimuli. Convulsions due to lead poisoning are seen especially in children, who usually present other evidences of plumbism. (Chapter 92.)

**4. Epilepsy of Unknown Cause.** After the most intensive and extensive search for a possible cause of attacks, in well over half the cases no cause can be found. This is the group that is usually labeled idiopathic. Patients in whom this diagnosis is made are treated medically and are followed closely. In such patients the development of symptoms and signs of an organic lesion will lead to a change in diagnosis to symptomatic epilepsy.

#### PROCEDURE WITH PATIENTS SUFFERING SEIZURES

A history of recurrent attacks of loss of consciousness or awareness associated with abnormal movements or confusion is usually sufficient to establish a diagnosis of epilepsy. In such patients a very thorough history, a complete physical and neurologic examination, examination of the visual fields, and laboratory study, including x-ray examination of the skull and an electroencephalogram, should be done. The results of these essential procedures will determine whether the disorder should be labeled idiopathic epilepsy, or whether further procedures need be instituted.

The history should be particularly searching in regard to epilepsy in the family history, occurrence of head trauma or infections in the past, and careful description of the seizure itself, including prodromata, aura, manifestations during the seizure, and the postictal period. The presence of seizures in the family history bespeaks for a diagnosis of idiopathic epilepsy. Head trauma of

a serious nature, followed at a suitable interval (several weeks to two years) by seizures, indicates that an injury may have given rise to the convulsions. Unusual prodromata or aura, especially of a focal nature, may indicate the presence of a localized lesion in the brain. Similarly, the description of a focal convulsive movement, especially at the onset of the seizure, indicates the high probability of a localized cerebral lesion. A transient monoplegia or hemiplegia in the postictal period also has considerable significance as to localization of a lesion. The presence in the history of other neurologic symptoms such as headache, localized paralysis, or mental changes often indicate that special diagnostic studies should be conducted. ~~A complete physical examination~~, with particular stress on the nervous system, is mandatory in each case of epilepsy. The findings can act as clues to the legion of conditions that are associated with epilepsy. The presence of protuberances over the skull may suggest an underlying pathologic condition. Vascular nevi over the body, especially over the face and in the retina, may be associated with vascular abnormalities within the skull. Small tumors, often pedunculated, distributed over the body surface bring to mind the diagnosis of Von Recklinghausen's disease, and when associated with seizures may indicate an intracranial glioma or neurofibroma. Sebaceous adenomas of the face in the typical butterfly distribution point to the diagnosis of tuberous sclerosis. The presence of cranial nerve findings may point to a diagnosis; thus a sixth nerve paralysis is often associated with increased intracranial pressure. Localized weakness, difference in reflexes, or the presence of abnormal reflexes such as a Babinski response, are all of potential localizing value. Coupled with the history, such findings in the examination will often yield a localizing as well as an etiologic diagnosis.

The question of ~~laboratory procedures~~ to be done in cases of epilepsy is one to be answered only on the basis of the previous findings. ~~X-rays of the skull~~ should be done in all cases. Findings of significance in regard to increased intracranial pressure include erosion of the clinoid processes, increase in the cortical markings, and separation of the sutures. Hyperostoses, erosions of the skull, abnormal vascular markings, and intracranial calcifications are other points of importance that may appear on skull x-rays. Be-

cause of the frequency of cerebral metastases from primary carcinoma of the lung, films of the chest should be made in all patients suspected of having intracranial neoplasms.

~~X~~ Lumbar puncture is a procedure that can be of tremendous value in the elucidation of the causes of epilepsy. If the patient has been hospitalized for study, then a lumbar puncture should be done. If the history, neurologic examination, or skull x-rays show any abnormality, especially if it is suggestive of a focal lesion in the brain, then a lumbar puncture is mandatory. Of special importance is the determination of the pressure, cell count, total protein, and serologic tests. An increased pressure points to an expanding intracranial lesion. An abnormal cell count is often indicative of an infectious process associated with the convulsions. An elevation in total protein (greater than 100 mg. %) suggests the diagnosis of a tumor. If the pressure is normal but other symptoms or signs point to a localized brain lesion, a pneumoencephalogram may be done. If, in addition to localizing signs, the patient shows signs of increased intracranial pressure, whether by papilledema or high cerebrospinal fluid pressure, then a ventriculogram is preferred to a pneumoencephalogram. The visualization of the cerebral ventricles by these procedures may be of particular help to a neurosurgeon from the point of view of location of the lesion and surgical approach to it.

~~X~~ The electroencephalogram is a test which is routinely employed in the definitive diagnosis of cases with epilepsy. The test is not absolutely conclusive, since the electroencephalogram may be normal in some patients, particularly if the seizures are relatively infrequent. The test is of particular value in diagnosis of petit mal, for here clinical or subclinical attacks are apt to be frequent enough to register during the electroencephalographic test. Abnormal electric waves may manifest themselves in other types of epilepsy during the interseizure period and thus aid in the diagnosis, either in demonstrating focal or generalized abnormalities of cortical activity.

Other laboratory tests that should be used routinely include examination of the urine and fasting blood sugar. Other examinations which may be indicated are determination of the blood calcium and a glucose tolerance test.

The procedure in cases of epilepsy is particularly tempered by the age of the patient. Up

until early adulthood the plan should be outlined as before. Most cases in this age group turn out to have idiopathic epilepsy. As one approaches ~~the older age groups~~, the incidence of idiopathic epilepsy drops off and the occurrence of symptomatic epilepsy increases. Thus the appearance of convulsions past middle age should be presumptive evidence of a diagnosis of brain tumor until every effort has been made to rule it out. However, in the last analysis each case must be dealt with on an individual basis, subsequent procedures depending on the previous findings.

The localizing significance of the more common types of seizures is indicated in table 9. The most

Table 9  
LOCALIZING VALUE OF VARIOUS TYPES  
OF SEIZURES\*

Clinical Type of Seizure	Localization
Generalized.....	None
Jacksonian.....	Pre-Rolandic area
Adversive.....	Frontal
Tonic postural.....	Brain stem
Somatic sensory.....	Post-Rolandic area
Visual.....	Occipital
Auditory.....	Temporal
Olfactory.....	Temporal
Dreamy state.....	Temporal

\* Adapted from Penfield and Erickson.

Table 10  
CAUSES OF CONVULSIONS IN DIFFERENT  
AGE GROUPS

Age of Onset	Probable Cause
Infancy 0-2 yr....	Congenital, abiotrophy, birth injury
Childhood 2-10 yr....	Birth injury, trauma, infectious or febrile thrombosis, idiopathic
Adolescence 10-18 yr....	Idiopathic, trauma, congenital
Youth 18-35 yr....	Trauma, neoplasm, idiopathic
Middle age 35-60 yr....	Neoplasm, trauma
Senescence 60- yr....	Cerebrovascular, neoplasm

frequent causes of convulsions in different age groups are presented in table 10, which is concerned only with the recurrent convulsive states related to primary organic disorders of the nervous system. Additional causes of convulsions include most of the disorders capable of causing syncope (Chapter 7) or coma (see p. 91).

## PARALYSIS

H. Houston Merritt and Daniel Sciarra

Paralysis, by general use, has come to mean partial as well as complete palsy. It encompasses all varieties of weakness of voluntary movement, and is to be considered apart from states of general weakness or debility. Accurate diagnosis usually depends less upon the degree of paralysis than upon its nature, distribution, and associated manifestations. To a great degree the nature of the paralysis is dependent upon the part of the motor system involved. When the motor system is involved at the cortex or anywhere along the course of the pyramidal tracts, the consequent paralysis is called upper motor neuron in type. Spasticity, increased deep tendon reflexes, and the presence of abnormal reflexes often accompany this type of paralysis. When the disease process involves the motor system at the anterior horn cells, at the motor nerve roots, or at the peripheral nerves, then the paralysis is called lower motor neuron in type. Flaccidity and decrease in deep tendon reflexes are concomitant features of lower motor neuron weakness. Atrophy of muscles also tends to be prominent. Paralysis of muscles due to disturbance at the motor end-plate, as in myasthenia gravis, is usually intermittent in type and is not associated with changes in reflexes or in muscle mass. Intrinsic disease of the muscles, as in progressive muscular dystrophy, may lead to muscle weakness. The muscles may undergo atrophy or evidence a pseudohypertrophy. Reflex loss may occur, usually paralleling loss in muscle substance.

The diagnostic consideration of paralysis may be simplified by the following subdivisions which relate to the location and distribution of the weakness:

**1. Monoplegia.** This term is limited to those affections in which one limb, be it leg or arm, is weak or completely paralyzed. It does not refer to isolated muscle or nerve paralyses in either arm or leg.

**2. Hemiplegia.** This condition is the most commonly occurring paralysis and refers to loss of strength in arm, leg, and sometimes the face on one side of the body.

**3. Paraplegia.** Paraplegia indicates a weakness or paralysis of both legs. It is most commonly found in spinal cord disease.

**4. Quadriplegia.** This indicates weakness of all four extremities and usually signifies a severe or long-standing process.

**5. Isolated Paralyses.** This term refers to weakness localized to one or more muscle groups.

## MONOPLEGIA

Patients complaining of weakness of one extremity are often found on physical examination either to have unnoticed weakness in another limb or weakness of isolated muscle groups in the extremity complained of. Moreover, ataxia, sensory disturbance, or pain in an extremity will often be interpreted by the patient as weakness, as will the mechanical limitation imposed by arthritis or the rigidity of Parkinsonism.

In general the presence or absence of atrophy in a monoplegia can be of considerable diagnostic help.

**1. Paralysis Without Muscular Atrophy.** Long-continued disuse of a limb may lead to atrophy, but this usually is not marked and electric stimulation of the muscles is normal.

The most common cause of monoplegia without muscular wasting is a lesion in the corticospinal tract in the brain or spinal cord. A vascular lesion (thrombosis, hemorrhage, or embolus) in the brain, brain tumor, brain abscess, or cerebral trauma may produce a monoplegia; but, more commonly, such lesions produce a weakness of both extremities on one side of the body. Multiple sclerosis and spinal cord tumor early in their course may cause a paralysis of one extremity, usually the leg. Weakness due to damage to the corticospinal tract is usually accompanied by spasticity, increased reflexes, and an extensor-plantar response. The diagnosis of the causes of a monoplegia without atrophy depends upon the history and the other findings on examination. Sudden onset of weakness usually indicates a cerebral vascular accident while slow progressive increase in weakness indicates an expanding lesion in the brain or spinal cord. The differential diagnosis between a monoplegia due to a lesion in the brain and that following an injury to the cord is made from the associated findings as in the case of a hemiplegia (see below).

Hysterical paralysis of one arm or leg also occurs without the presence of atrophy. The inconstancy of the paralysis may often be betrayed by testing individual muscles. "Improper flow" of power is an important diagnostic sign of a hys-

terical paralysis. Thus a patient with a hysterical paralysis of the arm will make great effort at moving the shoulder and trunk muscles when asked to move the fingers or forearm. Sensory findings of bizarre nature, often glove or stocking in distribution, will often reveal the cause of the disability. In distinguishing a hysterical paralysis from one of cerebral organic origin, the presence of associated movements in the latter type may be of great importance. Thus a patient with a cerebral monoplegia, while yawning or moving an unaffected limb, may note movement in the paralyzed leg or arm.

**2. Paralysis with Muscular Atrophy.** This group includes all cases of leg or arm paralysis with muscular atrophy. It is important in such cases to determine whether all the affected muscles are supplied by an individual nerve or by certain spinal segments. In addition to atrophy and decreased electric response, the limb will tend to show decreased tendon reflexes and, at times, muscle fibrillation. This latter usually means disease within the spinal cord.

**BRACHIAL PALSY.** Paralysis of one arm which is noticed at birth, or in weeks thereafter, is usually due to an injury to the brachial plexus during delivery. If the upper roots of the brachial plexus are affected (Erb's palsy), the weakness and atrophy are most severe in the shoulder girdle and upper arm. Weakness of the hand and forearm indicate damage to the lower roots (Klumpke's palsy). Rarely, a monoplegia in a child may be cerebral in origin; the reflexes may then be expected to be increased.

Traumatic involvement of the brachial plexus occasionally occurs in others than infants, but the symptoms and signs are the same. Metastatic or upper mediastinal tumors may involve the brachial plexus with the same result. A cervical rib or a tight scalenus anterior muscle may press on the brachial plexus and cause a paralysis or weakness of isolated muscle groups in one arm. The presence of pain, sensory loss, and the associated circulatory changes are points indicative of compression of the plexus by a cervical rib or scalenus anterior muscle. There is also tenderness in the supraclavicular fossa. X-rays of the cervical spine will show a cervical rib if it is present.

**AMYOTROPHIC LATERAL SCLEROSIS,** or progressive spinal muscular atrophy, is a disease in which there are degenerative changes in the an-

terior horn cells of the spinal cord with weakness and atrophy of muscles. In the late stages of the disease the weakness and wasting of the muscles is generalized, but in the early stages they may be confined to one extremity. Fibrillations of the muscles are common. Tendon jerks may be exaggerated if the atrophy is not marked. Sensory findings are absent.

**ACUTE ANTERIOR POLIOMYELITIS** not infrequently damages an isolated segment of the spinal cord and causes an atrophic monoplegia. The acute onset accompanying a febrile illness, tenderness of the muscles to pressure, and the pleocytosis in the cerebrospinal fluid are factors which favor the diagnosis of acute anterior poliomyelitis.

**SYRINGOMYELIA.** Destruction of the ventral horn cells in syringomyelia is accompanied by an atrophic paralysis of the muscles supplied by the affected cord segments. The cervical enlargement is most commonly the site of the syrinx. Thus, paralysis and atrophy of one upper extremity is frequently an early sign of the disease. Scars of previous burns and other injuries, the characteristic loss of pain and temperature sense in a segmental distribution, scoliosis, and signs and symptoms of damage to the long tracts in the spinal cord are important points in the diagnosis of syringomyelia. An intramedullary tumor may at times produce a symptom-complex similar to that of syringomyelia.

**RUPTURED INTERVERTEBRAL DISK.** A tumor originating in the spinal meninges may compress nerve roots and cause an atrophy in one limb. A more common cause of compression of one or more of the roots which innervate the extremities is a ruptured intervertebral disk. Occasionally found in the cervical region, but more commonly in the lumbar area, the syndrome, when fully developed, is easily recognized. There is usually a history of a minor or severe injury to the spine with repeated attacks of pain in the affected extremity. The pain is usually increased by activity and alleviated by rest. On examination there is little or no atrophy and the weakness is more apparent than real. Movements of the affected extremities are limited, since they are apt to produce pain. There is an alteration of the normal configuration of the spine, pain on stretching the nerve root in such maneuvers as straight leg raising, and tenderness to pressure over the affected vertebral area. In addition, there may be

hypesthesia or anesthesia of the skin innervated by the affected root, and diminution or loss of the appropriate tendon reflex. The cerebrospinal fluid protein content may be slightly or moderately elevated.

MUSCULAR DYSTROPHY may rarely start in one extremity. Accurate diagnosis will depend upon muscle biopsy or await the development of the typical symmetric pattern of muscular weakness.

### HEMIPLEGIA

Weakness or paralysis of the arm and leg on the same side of the body is described by the term hemiplegia. A hemiplegia, with rare exceptions, is due to an injury to the corticospinal tract. The site of injury to the corticospinal tract can be deduced from the associated neurologic findings.

**Location of Lesion Producing Hemiplegia.** Lesions of the corticospinal tract in the cerebral cortex or internal capsule usually produce a paralysis or weakness of the face, arm, and leg of the opposite side. The occurrence of convulsive seizures, or the presence of a defect in speech (dysphasia), a cortical type of sensory loss (astereognosis, loss of two-point discrimination, etc.), or defects in the visual fields are all factors suggesting a cortical location for the lesion.

Lesions of the corticospinal tract in the upper portion of the brain stem may cause a paralysis of the face, arm, and leg of the opposite side. The lesion in such cases is localized by the presence of a paralysis of the muscles supplied by the oculomotor nerve on the same side as the lesion (Weber's syndrome).

Lesion of this tract in the middle portion of the brain stem produces a paralysis of the opposite arm and leg. This is usually accompanied by a paralysis of the facial muscles on the same side as the lesion, and paralysis of lateral gaze to this side (Millard-Gubler syndrome).

Lesions of the tract in the lowermost portion of the brain stem causes a paralysis of the opposite arm and leg. In such cases there is usually a paralysis of the palate or tongue on the same side as the lesion.

Lesion in the cervical portion of the spinal cord is a rare cause of homolateral hemiplegia. More commonly such lesions result in a quadriplegia. If, however, the damage is localized to one lateral half of the cord, there is a homolateral hemiplegia and a loss of pain and temperature sense

in the opposite half of the body (Brown-Séquard syndrome).

Muscular atrophy rarely occurs in the hemiplegia which follows lesions of the corticospinal tract. When the motor cortex and the adjacent portion of the parietal lobe are injured in infancy, the normal development of the muscles and skeletal system are impaired on the side opposite to the lesion. In the hemiplegia due to spinal cord injury there is usually an atrophy of the muscles at the level of the lesion as result of damage to the ventral horn cells.

**Causes of Hemiplegia.** A discussion of the morbid entities which may produce a hemiplegia is simplified by considering the mode of onset of the symptoms.

1. **SUDDEN ONSET.** A hemiplegia of sudden onset is usually the result of a cerebral vascular accident. The differential diagnosis between cerebral thrombosis, hemorrhage, or embolism cannot be made from the extent or severity of the paralysis. Focal premonitory signs and retention of consciousness favor the diagnosis of cerebral thrombosis. Convulsions and coma at the onset or headache and stiffness of the neck in non-comatose patients are more common in cerebral hemorrhage. A cerebral embolus is the most probable cause of the hemiplegia if there is severe rheumatic heart disease, auricular fibrillation, or a recent coronary thrombosis. Trauma to the head with cerebral contusion and laceration may lead to a hemiplegia. The cause of the hemiplegia in such cases is usually obvious, but difficulty may be encountered in differentiating the effects of the acute injury from some of the sequelae of head injury, notably subdural or extradural hematoma. Typically, hemiplegia due to cerebral laceration should be most severe immediately following the injury. The common sequence of events in patients with an extradural hematoma is a period of coma of short duration followed by a lucid interval for several hours and then relapse into coma with a hemiplegia. This sequence of events does not occur always, because the coma which is due to the initial injury may be prolonged and merge with the coma resulting from the pressure on the brain by the expanding hematoma. If x-ray of the skull shows a fracture across the groove of the middle meningeal vessel, a presumptive diagnosis of extradural hematoma should be made and an exploratory operation performed. The diagnosis of a subdural hema-

toma is often difficult. Fluctuations in the level of consciousness are common in patients with this type of lesion and, when they occur, a trephine exploration in the parietal region of both sides of the skull is mandatory (see p. 1530). Trauma to the spinal cord at a high cervical level may also produce a hemiplegia, though quadriplegia is more likely.

Acute infections of the meninges or cerebral parenchyma may be accompanied by a sudden hemiplegia. The paralysis in these cases is usually due to thrombosis of an inflamed meningeal or cortical vessel. Although hemiplegia may occur in any of the acute purulent meningitides, it is more common in the chronic or subacute forms (tuberculous, syphilitic). Hemiplegia may be a symptom of the virus or postinfectious encephalitides. Rarely, a hemiplegia may develop suddenly in patients with multiple sclerosis or other demyelinating diseases. The diagnosis in these cases depends on the history, associated neurologic findings, and the results of examination of the cerebrospinal fluid.

**INFANTILE HEMIPLEGIA.** One-sided weakness in the very young may exist from birth as the result of birth trauma or cerebral maldevelopment. The latter is more often a quadriplegia and is accompanied by choreoathetoid movement of the affected extremities. In these cases the motor difficulty may be evident immediately after birth, but more commonly it does not appear until the second or third year of life, when the child will not be able to accomplish what is expected of it at this stage of development. The cases with paralysis of only one arm or leg may be difficult to separate from hemiplegias occurring later in infancy or childhood. Ultimate distinction may depend on the fact that the patients with a spastic hemiplegia due to birth injury or cerebral maldevelopment never developed normal motor performance, whereas those with an acquired hemiplegia were at one time able to function at a certain level and then lost that ability. The most common cause of acquired infantile cerebral hemiplegia is a cerebral vascular lesion (arterial or venous) which occurs in connection with an infection or febrile illness. Coincident with the fever there are convulsive seizures followed by a spastic hemiplegia.

**2. GRADUAL ONSET.** The slow development of a hemiplegia usually indicates that there is an

expanding lesion in the brain—neoplasm, abscess, or subdural hematoma.

**CEREBRAL NEOPLASM.** The classic symptoms of an intracranial tumor are headache, nausea, and vomiting. These symptoms usually do not develop until the late stage of the disease, and the diagnosis should be established before this stage is reached in a patient with a slowly progressing hemiplegia or other focal neurologic signs. Diagnostic aids include examination of the fundi for swelling of the optic disks; testing of the visual fields for enlargement of the blind spot or defects in the peripheral field; electroencephalogram for the presence of focal abnormalities; x-rays of the skull for signs of increased intracranial pressure (increase in convolutional markings, enlargement of the sella turcica, or erosion of the clinoid processes), displacement of the pineal gland, erosion or overgrowth of the bones of the skull, and the presence of abnormal calcifications; lumbar puncture with measurement of the pressure and examination of the fluid. This is usually safe in the absence of choked disks. An increased pressure or a protein content greater than 100 mg. % strongly indicates the diagnosis of a tumor. If the diagnosis of a tumor cannot be established by the above methods, pneumoencephalography by either the lumbar or ventricular route, or cerebral angiography, will be necessary. Ventriculography is preferred to lumbar encephalography if there are signs of increased intracranial pressure.

**CEREBRAL ABSCESS.** The signs and symptoms of cerebral abscess are exactly similar to those of a cerebral neoplasm. Fever is not present in patients with a brain abscess unless there is activity in the focus which has given rise to the abscess. The diagnosis of abscess is presumed whenever there is a focus of infection in the skull, such as mastoiditis, sinusitis, osteomyelitis, or dural sinus thrombosis. A pleocytosis in the cerebrospinal fluid is in favor of the diagnosis of an abscess.

**SUBDURAL HEMATOMA.** The diagnosis of an acute subdural hematoma should be presumed in every patient who has had a recent head injury and who does not respond to the routine treatment. This is particularly true if a hemiplegia develops or if there are fluctuations in the level of consciousness from day to day. An exploratory trephine opening should be made in one or both temporal regions of the skull in all such cases.

The diagnostic considerations of a patient with a chronic subdural hematoma are the same as for a patient with an intracranial neoplasm, since the symptomatology and clinical signs are identical.

**CERVICAL CORD NEOPLASM.** Cervical spinal cord neoplasm, usually intramedullary, may produce a hemiplegia. In such cases a homolateral hemiplegia may be expected to be coupled with contralateral loss of pain and temperature sensibility below the level of the lesion. The diagnosis of a spinal cord tumor is established by x-rays of the spine, by the testing of cerebrospinal fluid dynamics for subarachnoid block, and by myelography. Syringomyelia may produce this picture and, except for longer course, may be indistinguishable from intramedullary tumor.

**MULTIPLE SCLEROSIS.** Multiple sclerosis in its varied and irregular course may present a picture of spastic hemiplegia. If this is the presenting symptom, diagnosis cannot be made with certainty until the other more usual signs such as nystagmus, ataxia, and intention tremor develop.

### PARAPLEGIA

This term is used to indicate paralysis of both legs. Clinically, it is instructive to discuss separately the paraplegias of infancy and of later life.

**1. Infantile Paraplegia.** Difficulty in walking or in starting to walk is a common pediatric problem. It may be associated with general system diseases such as rickets or may be indicative of mental deficiency or, more commonly, of some neurologic disease.

Congenital spastic paralysis accounts for a majority of the cases of infantile paraplegia. Present at birth or shortly thereafter, this condition usually predicates some maldevelopment of the fetal cerebrum. The paraplegia that may follow birth injury or neonatal cerebral anoxia is in no way clinically distinguishable from congenital spastic paraplegia. Mental deficiency may accompany these conditions.

Thrombosis of the superior sagittal sinus may occur in association with infection or febrile illness, and a picture of spastic paraplegia may result. Areas of infection in or about the head may act as precipitants of the thrombosis.

Congenital malformation of the spinal cord and its coverings are also associated with paraplegia. A spina bifida or spina bifida occulta often act as clues indicating disease of the underlying cord. This may vary from a simple meningocele

to a meningomyelocele or maldevelopment of the lower segments of the cord.

Acute anterior poliomyelitis may give a flaccid paraplegia in infants. Lumbar puncture early in the course of the illness is of great aid in establishing the diagnosis.

Muscular dystrophy commonly has its onset in childhood with weakness of the pelvic girdle and consequent difficulty in walking. The muscles of the shoulder girdle are usually affected also. The disease is limited to the muscles; proximal groups are affected more than distal. Pseudohypertrophy of some muscles may be of help in diagnosis. The diagnosis is established by muscle biopsy.

**2. Paraplegia of Sudden Onset: EPIDURAL ABSCESS.** Epidural abscess, an acute surgical emergency, is a metastatic focus of infection in the epidural space secondary to a pyogenic focus in the skin or elsewhere in the body. The abscess may cause compression of the spinal cord and permanent damage to the spinal cord if the abscess is not evacuated before there is occlusion of the vascular supply of the cord. The diagnosis is established by lumbar puncture. The needle is inserted slowly and suction applied. If pus is found in the epidural space, the needle should be withdrawn and operation performed. If no pus is found in the subdural space, the subarachnoid space is punctured. There is partial or complete subarachnoid block and there is a pleocytosis in the fluid.

**SPINAL TRAUMA.** Hematomyelia represents hemorrhage into the cord, usually following some sort of spinal injury. Paraplegia is usually present at the onset. With resorption of the hemorrhage, the symptoms may be of the Brown-Séquard type.

Trauma to the spinal cord may result in a complete section of the cord with a resultant paraplegia. This may be transient or lasting, depending on the degree of cord damage, and is usually associated with marked sensory changes. If fracture dislocation of the spine is evident in the x-ray films or if subarachnoid block is present, laminectomy should be performed to decompress the cord.

**ACUTE TRANSVERSE MYELITIS.** Acute transverse myelitis gives rise to a sudden paraplegia. Its causes may be various. Some cases are connected with an acute attack of multiple sclerosis. Others are related to virus infections and post-

infectious encephalomyelitides, and others are of unknown cause. Involvement of the spinal meninges by syphilis usually produces a slowly developing paraplegia, but occasionally a flaccid paraplegia may develop suddenly as the result of thrombosis of inflamed spinal vessels.

**TUMORS.** Tumors which invade the vertebrae or the epidural space may cause a sudden paraplegia by encroachment on blood vessels. This is most commonly seen with metastatic carcinomas and the lymphogenous tumors or Hodgkin's disease. Surgical intervention will not be of much value in such cases, since the damage to the spinal cord is due to occlusion of its blood supply and not to compression of the cord.

**HYSTERICAL PARAPLEGIA.** Functional paraplegia is often of sudden onset. The absence of sensory findings or their bizarre distribution will often be of great aid in the diagnosis. Many cases, however, that are labeled functional turn out to be organic. Multiple sclerosis may be particularly difficult to exclude.

**3. Paraplegia of Gradual Onset : SPINAL NEOPLASMS.** When both legs are involved in a slowly progressive weakness, neoplasm of the spinal cord is to be considered likely and must be ruled out before other possibilities are considered. Pain is a likely accompaniment of cord tumor. In the aged, pain and paraplegia are likely to indicate metastatic cord tumor. The presence of a block or lumbar puncture, an elevated cerebrospinal fluid protein, and a positive myelogram all tend to substantiate the diagnosis. Occasionally, cord tumor may cause a sudden paraplegia by occlusion of a blood vessel.

**PARASAGITTAL TUMORS.** Parasagittal tumors (meningiomas or gliomas) usually cause a hemiplegia, but because of their location they may cause a slowly progressive paraplegia. The other features of cerebral neoplasm, including headache, papilledema, and seizures, will usually elucidate this diagnosis.

**MULTIPLE SCLEROSIS.** Spastic paraplegia is a frequent symptom in the course of multiple sclerosis. When it is the presenting symptom, the diagnosis of a spinal cord neoplasm must be excluded by the appropriate tests. In middle-aged or elderly patients, combined system disease will have to be ruled out. Usually, however, the patient will present other evidence of dissemination such as nystagmus, speech disturbance, and history of remissions.

**COMBINED SYSTEM DISEASE.** Combined system disease, a common cause of paraplegia, is usually slow and insidious in onset. Paresthesias of the hands and feet are a constant accompaniment of subacute combined degeneration. Marked involvement of the legs, with minimal or no involvement of the arms, is also a common feature. The diagnosis is established by the finding of a macrocytic anemia, gastric achylia, and the response to liver therapy.

**SYRINGOMYELIA.** Syringomyelia not infrequently will cause a paraplegia of slow progression. Sensory loss of a segmental type (often of a dissociated nature with pain and temperature sensation being lost and touch preserved), atrophy, trophic skin lesions, and at times Charcot joints are characteristics of this disease. Because of the central location of the syrinx within the cord, an intramedullary cord tumor often cannot be distinguished from syringomyelia except by its more rapid progression.

**POLYNEURITIS.** Polyneuritis usually involves all extremities. Weakness of the legs may be the first sign, especially in the so-called alcohol-vitamin deficiency type and in Landry's or ascending polyneuritis. The gradual or subacute evolution of symptoms, muscular weakness, sensory loss, absent reflexes, and tenderness of the muscles and nerve trunks to pressure are characteristic signs of polyneuritis.

**AMYOTROPHIC LATERAL SCLEROSIS.** Amyotrophic lateral sclerosis usually involves both the arms and legs but it may start in the lumbar cord, giving a paraplegia with atrophy, fibrillation, and absence of sensory findings. The diagnosis in such cases must await the development of signs and symptoms in the upper extremities.

**TABES DORSALIS.** Tabes dorsalis may be accompanied by a host of symptoms and signs, among which may be weakness of the legs. Often this weakness is more apparent than real, incoordination accounting for most of the leg difficulty. The serologic tests are positive for syphilis in the blood and cerebrospinal fluid. A history of lancinating leg pains or gastric crises, the presence of Argyll-Robertson pupils, and the loss of position sense and reflexes point to tabes dorsalis.

**FRIEDREICH'S ATAXIA.** Friedreich's ataxia may be a cause of paraplegia in children or young adults. Deformities of the feet may be expected. Plantar responses are extensor, knee jerks are

absent, and there is ataxia of the legs. Nystagmus may be present, as well as a monotonous speech. The arms may be involved with some ataxia. Other members of the family may show a similar syndrome.

**PERONEAL MUSCULAR ATROPHY.** Peroneal muscular atrophy is a heredofamilial disease. The muscles supplied by the external popliteal nerve are affected first and dorsiflexion of the toes and feet is weak. The weakness extends to the other muscles of the lower extremity. The ankle jerks are lost and there is an impairment of sensation in the distal part of the extremity. Clubfeet and a "stork leg" appearance are characteristic of the disease.

### QUADRIPLEGIA

In infants, quadriplegia is more likely to represent diffuse disease of the muscles or the central nervous system. A common cause in infants is congenital defect of the cortex, leading to a spastic quadriplegia. This is usually evident from birth or shortly thereafter, and, because of the usually extensive cerebral damage, mental deficiency is also present. Muscular dystrophy, which is also a common cause of quadriplegia in the young, is characterized by weakness of pelvic and shoulder girdles, flaccid muscles which are at times pseudohypertrophic in the calf and biceps region, lordotic posture, and a waddling gait.

Schilder's disease and amaurotic familial idiocy (Tay-Sachs disease) also may lead to disability and weakness of all four extremities. The typically progressive cerebral picture in Schilder's disease and the presence of the cherry red spot in the fundi of patients with Tay-Sachs disease are helpful in distinguishing these afflictions. Acute anterior poliomyelitis may produce a sudden quadriplegia in the young. Its diagnosis again will depend on cerebrospinal findings and isolation of the virus from the stool.

In adults, paralysis of all four limbs focuses attention on the cervical cord. Acute myelitis, caused by multiple sclerosis or associated with a nonspecific demyelinization or myelomalacia, may affect the cervical cord, leading to weakness of all four limbs. Differentiation between these causes may be difficult and the diagnosis may have to await further episodes in the case of multiple sclerosis.

Trauma to the cervical vertebrae and thence

to the cord may produce a sudden quadriplegia. The diagnosis will often be obvious. Prognosis for life is poor if the disability does not begin to improve over a period of several weeks.

Acute anterior poliomyelitis is also a cause of sudden quadriplegia in adults. The febrile illness, the cerebrospinal findings, and the absence of sensory findings will establish the diagnosis.

Basilar artery thrombosis is a rare cause of sudden quadriplegia and is essentially incompatible with life.

Quadriplegia of gradual onset raises the suspicion of a focal lesion in the cervical cord. Tumor in this region is the possibility that must always be considered. A history of gradual progression may then be supported by x-ray changes in the cervical vertebrae, presence of block on spinal fluid dynamics, increase in cerebrospinal protein, and a positive myelogram.

Polyneuritis characteristically involves all four extremities. The peripheral distribution, lower motor neuron weakness, and sensory loss point to this diagnosis. The cerebrospinal fluid will often show a high total protein, especially in infectious polyneuritis.

Multiple sclerosis, syringomyelia, and amyotrophic lateral sclerosis may also lead to a gradual quadriplegia. The story of remissions and evidence of disseminated lesion will establish the presence of multiple sclerosis. Muscle atrophy, dissociated sensory loss, and trophic skin changes are a common accompaniment of syringomyelia. A general body dysmorphism may also be in evidence in many cases. Amyotrophic lateral sclerosis is distinctive because of the muscular wasting, the fibrillations, and the absence of sensory findings.

Repeated cerebral vascular accidents may present a picture of quadriplegia, usually accompanied by a pseudobulbar picture. A history of repeated vascular insults is common, with one hemiplegia being followed by another on the contralateral side. The patient then may exhibit weakness of all extremities, difficulty in talking and swallowing, and emotional instability.

### ISOLATED PARALYSIS

Paralysis of isolated muscle groups usually indicates a lesion of one or more peripheral nerves. The diagnosis of a lesion of an individual peripheral nerve is made on the presence of weakness or paralysis of the muscle or group of

muscles innervated by this nerve, and by the finding of an impairment or loss of cutaneous sensation in the area of its distribution. Complete transection or severe injury to a peripheral nerve is usually followed by atrophy of the muscles innervated by it, and loss of their tendon reflexes. Trophic changes in the skin, nails, and subcutaneous tissue may occur also.

A knowledge of the muscular and sensory function of each individual nerve is needed for a satisfactory diagnosis. Since lesions of the peripheral nerves are relatively uncommon in civil life, it is not practical for the general physician to keep all these facts in his memory, and a textbook of anatomy or a compendium on nerve injury should be consulted.

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## Section 3—Shortness of Breath and Cough

# 9

## Shortness of Breath

T. R. Harrison

### Regulation of Breathing

#### Relationship Between Dyspnea, Labored Breathing, and Respiratory Measurements

#### Conditions Causing Decrease in Vital Capacity

#### Conditions Causing Increase in Ventilation

#### Factors in the Production of Dyspnea

#### Effect of Labored Breathing

#### Clinical Types of Dyspnea in Relation to Differential Diagnosis

Dyspnea, or "shortness of breath," consists of an uncomfortable sensation—but not a pain—in the chest, associated with a feeling of a desire for forceful respiration. This subjective sensation is usually, but not invariably, accompanied by visibly labored breathing, and ordinarily a general parallelism exists between these phenomena. *It is possible that dyspnea is the result of the central perception of fatigue or tension arising in the respiratory muscles.* This is only a tentative concept, pending further evidence.

As a rule, dyspnea first appears during muscular effort, the patient later noting that less and less exertion is required to produce the sensation. After a time it may begin to appear at rest, either in the form of *orthopnea* (i.e., dyspnea which is aggravated by the recumbent posture), or *trepnopnea* (i.e., dyspnea which is more marked in one recumbent position than in others), or *Cheyne-Stokes respiration* (periodic dyspnea), or *paroxysmal seizures of dyspnea*, such as may occur in persons subject to bronchial asthma, cardiac asthma, and acute pulmonary edema.

In evaluating dyspnea the first decision to be made is whether in a given individual the symptom is of pathologic significance. Healthy persons are never dyspneic at rest, but any normal individual may become dyspneic upon undertaking sufficiently strenuous exercise. As a rule, shortness of breath sets in more readily in females than in males, in age than in youth, in obese subjects than in thin persons, and in those who lead sedentary lives than in those who are accustomed to physical exercise. Hence exertional dyspnea can only be considered as pathologic

either when an individual has progressive increase in dyspnea for a given effort, or when the degree of shortness of breath experienced for a given performance is definitely greater than that experienced by other individuals of the same sex, age, body build, and state of physical conditioning.

### REGULATION OF BREATHING

The respiratory center is probably capable of automatic rhythmicity, although this question is still debated. In any case, its activity is profoundly modified by various factors, which may be of either nervous or chemical origin. The chief chemical factors in the blood are the tensions of carbon dioxide and of oxygen, and the hydrogen-ion concentration. There is considerable evidence which suggests that each of the factors—increase in hydrogen-ion concentration and in carbon dioxide tension, as well as decrease in oxygen tension—tends to stimulate breathing by increasing the hydrogen-ion concentration of the respiratory center. Some respiratory physiologists hold that this is the sole chemical regulator; others believe that the several chemical factors act separately and differently. Anoxia stimulates the respiratory center by increasing its hydrogen-ion concentration, but depresses its sensitivity. In addition, oxygen deficiency stimulates the chemoreceptor mechanism of the carotid body.

The nervous factors which regulate breathing include reflex influences on the respiratory center arising in almost any part of the body, and also impulses arising from higher centers, which allow for a certain degree of voluntary control, and which are responsible for the effects of emotion on respiration. Of the numerous reflexes, the most important are those arising in the lungs and transmitted centrally via the vagus nerves. Other important reflexes arise in the skeletal

tissues (muscles and joints), for both active and passive movements of these structures produce increase in breathing which is not altered by blocking the venous return, but is abolished by blocking the afferent nerve pathways from the moving parts. Impulses also arise in the heart and in the great vessels, especially in the carotid arteries at their sites of bifurcation (carotid sinuses) and in the aortic arch. Changes in blood pressure in these structures are reflected by alterations of breathing, rises and falls in pressure causing depression and increase in amplitude, respectively.

Aside from the purely chemical and the strictly nervous regulation of breathing, there is an important combined mechanism by means of which chemical alterations in the carotid bodies may cause stimulation of the respiratory center through nerve pathways. This is the chemoreflex mechanism.

When a normal individual undertakes *strenuous* exercise, well-marked chemical changes occur in the blood (such as rise in lactic acid), and these may play a dominant role in stimulating the breathing. However, *very mild* exercise causes no such changes, and the moderate increase in respiratory minute volume which occurs under these circumstances is due to reflex effects from the moving parts and from increased pressure in either the right atrium or the great veins.

#### RELATIONSHIP BETWEEN DYSPNEA, LABORED BREATHING, AND RESPIRATORY MEASUREMENTS

Ordinarily, a dyspneic individual displays obvious evidence of labored breathing. When such evidence is lacking, the dyspnea is probably psychogenic in origin. Conversely, an unconscious patient may have markedly labored breathing, but cannot experience the sensation of dyspnea. Hence, any striking disproportion between the subjective phenomenon, dyspnea, and the objective manifestation, labored breathing, indicates a psychogenic disturbance as the likely cause for the discrepancy.

Labored breathing usually is accompanied by some increase in respiratory rate, and by some elevation of the volume of air breathed per unit of time. However, when for any reason there is obstruction to the airways, the breathing may be decidedly labored, and yet the rate and volume of respiration remain within the normal

range. Such a condition is spoken of as "wheezing," which implies not only labored but also audible breathing. The most common cause is bronchial asthma, but any condition which causes obstruction to the respiratory passages may produce the phenomenon. In a patient who is wheezing, the degree of dyspnea tends to parallel the degree of respiratory effort, but neither phenomenon is necessarily related to respiratory rate or amplitude. Under these circumstances the most satisfactory index as to the degree to which the breathing is labored is the intrapleural pressure. Comparison of this function with tidal air affords an index of the efficiency of breathing in experimental animals. Such measurements cannot ordinarily be carried out on dyspneic patients.

At first sight, the fact that a person may become dyspneic on holding the breath seems contrary to the idea that dyspnea represents the cortical reflection of fatigue in respiratory muscles. However, it should be remembered that some of the muscles of respiration are in some degree contracted, and others are stretched in all positions of the chest, and, consequently, that such muscles as are affected may become fatigued even when the breath is held. The equally paradoxical absence of dyspnea during the period of breath holding, following vigorous and prolonged hyperventilation, is explained by the lowered threshold of sensitivity of the respiratory center induced by the hyperventilation. This phenomenon is simply one of the manifestations of lowered acuity of the entire nervous system which, when hyperventilation is sufficiently pronounced, may proceed to the point of unconsciousness.

If the concept that dyspnea represents the cortical reflection of fatigue in the muscles of respiration is accepted, then the relation between dyspnea and labored breathing becomes clarified. The degree to which the breathing is labored depends on the degree to which the actual respiratory effort expended approached the maximum effort which can be expended. Thus any condition which reduces the maximum effort which can be expended tends to cause labored breathing, and this accounts for the appearance of dyspnea in subjects with diseases of the upper spinal cord and brain stem (e.g., bulbar poliomyelitis) or in states of profound muscular weakness (e.g., myasthenia gravis). Similarly, and

more commonly, any condition which increases the actual effort expended tends to cause dyspnea. Such conditions are of two types: those which interfere with the ready passage of air in and out of the lungs as the result of obstruction to the respiratory passages, and those which cause increased volume of breathing in relation to maximal volume. These two types of increased respiratory effort may now be considered in somewhat more detail.

Aside from the conditions which have been mentioned—psychogenic disturbances, grave muscular weakness, and obstruction to breathing—dyspnea and labored breathing tend to be proportional not only to each other but also to certain respiratory functions. A general relationship exists between them and the amount of air which is breathed (the respiratory minute volume or the ventilation), but the correlation is not close. Similarly, an inverse relationship exists between the degree of dyspnea and the maximum amount of air which can be breathed (the vital capacity), but this correlation likewise is not close. On the other hand, a rather striking parallelism exists between the degree of dyspnea and the expression

$$\frac{\text{amount of air actually breathed}}{\text{maximum amount of air which can be breathed}}$$

or  $\frac{\text{ventilation}}{\text{vital capacity}}$

In other words, dyspnea tends to become progressively greater (and the breathing more labored) as the actual volume of air breathed approaches the maximum volume which can be breathed in a given unit of time. (As already mentioned, this relationship does not hold true when the sensitivity of the psyche is markedly altered, when profound weakness of respiratory muscles is present, or when obstruction to the airways exists.) The problem of the pathogenesis of most types of dyspnea, therefore, resolves itself largely into two questions: (1) What are the conditions which diminish the vital capacity? and (2) What are the conditions which increase the ventilation?

The expression  $\frac{\text{ventilation}}{\text{vital capacity}}$  (or the ventilation index) represents the simplest formulation of the principle that dyspnea tends to appear when the actual ventilation becomes more than a certain proportion of the maximum possible ventilation. The measurements require only

slight coöperation on the part of the patients. However, the vital capacity is proportional to the maximum ventilation only when the factor of obstruction is absent, and recent studies indicate that this factor is present in some degree in most of the conditions which cause dyspnea. Hence the more recent procedure, which utilizes the maximum breathing capacity (p. 1391), is more accurate, although it requires a greater degree of coöperation on the part of the patient, who must breathe maximally for a longer period of time. For the sake of simplicity, the discussion to follow will be centered, in the main, around ventilation and vital capacity, but the importance of the obstructive factor should not be overlooked.

### CONDITIONS CAUSING DECREASE IN VITAL CAPACITY

**1. Upward displacement of the diaphragm** may result from physiologic states such as the recumbent position and pregnancy, or from pathologic conditions, including ascites, tympanites (marked gaseous distention of the intestines), and diaphragmatic paralysis.

**2. Disorders of the pleural cavities** due to extensive adhesions, fluid, pneumothorax, or herniation of abdominal contents interfere with the expansion of the lungs and thus reduce the vital capacity.

**3. Primary diseases of the lungs** due to whatever cause will, if sufficiently extensive, have a similar effect. In general, the acute disorders are more likely to produce severe dyspnea than are the chronic diseases. Hence, pneumonia and acute atelectasis are especially important. However, other more chronic disorders may produce this symptom. Any disease such as bronchial asthma, bronchial carcinoma, mediastinal aneurysm or tumor, or extensive bronchiectasis with thick secretion, which produces sufficiently severe obstruction to trachea or bronchi, will produce dyspnea as the result of obstruction of the air passages. In such instances lowering of the vital capacity plays a role but is probably of less importance than respiratory stimulation. Such stimulation is apparently due to elevation of arterial carbon dioxide tension in some instances, but in others the mechanism is uncertain.

Other important diseases of the lungs tending to produce decrease in vital capacity and consequent dyspnea include emphysema, extensive

pulmonary fibrosis from any cause, widespread miliary tuberculosis, diffuse pulmonary (miliary) carcinomatosis, and advanced disease of the pulmonary arteries such as occurs in Ayerza's disease. In these disorders the dyspnea may be related not only to decline in vital capacity but also to stimulation of breathing as the result of anoxia, of elevation of carbon dioxide tension, or of reflexes originating in the lungs.

In all of these disorders the respiratory stimulation may be slight but, in general, the decline in vital capacity is sufficiently severe to produce well-marked dyspnea during exertion, which is attended by increased ventilation and mild to moderate dyspnea at rest, even though the resting respiratory minute volume may remain within normal limits or be only slightly increased.

**4. Secondary disorders of the lungs** resulting from cardiac disease include passive congestion, which is the most important and frequent, as well as those dangerous and often fatal complications—acute pulmonary edema and infarction of the lungs. These disorders are particularly important in causing dyspnea because they not only lead to well-marked decline in vital capacity but also are especially likely to stimulate respiration.

#### CONDITIONS CAUSING INCREASE IN VENTILATION

Of the physiologic causes of respiratory stimulation, muscular exertion, which has already been discussed, is of first importance.

Among the pathologic conditions the various chemical alterations of the arterial blood, such as anoxia due to congenital cardiac disease, or acidosis complicating diabetes, are important; but since decline in vital capacity often does not occur, the degree of dyspnea at rest may be relatively slight, unless the chemical changes are of extreme degree.

Any extensive disorder of the lungs tends to cause respiratory stimulation. Congestion, either active (pneumonia) or passive (as the result of congestive heart failure) is particularly important because it not only causes well-marked decline in vital capacity brought about by swelling and rigidity of the lungs, but also seems to have a special effect in causing respiratory stimulation by means of the pulmonary vagal reflex. Aside from those conditions which cause a high degree of bronchial obstruction, the most severe dyspnea which is observed, clinically, is

in patients with active (pneumonia) or passive (heart failure) congestion of the lungs. When, in addition to the congestion, edema or infarction is added, arterial anoxia develops, chemical stimulation is added to the preexisting reflex stimulation, and extreme dyspnea supervenes.

Since the most common and important cause of long-standing severe dyspnea is congestive heart failure, a further brief discussion of this subject is indicated. When heart failure is beginning, dyspnea usually occurs only on exertion. Any condition, such as muscular exercise, which increases the venous pressure in the right side of the heart and the great veins, tends to cause slight to moderate reflex stimulation of breathing. Likewise, the reflex effect of muscular movements causes increase in breathing. These effects, when acting on the normal individual with an unaltered vital capacity, are slight. When, however, a patient with congestive heart failure is concerned, the vital capacity is already reduced, and these factors may cause severe dyspnea as the result of such a simple activity as walking across the room.

As heart failure proceeds, dyspnea begins to occur at rest, and may appear in a number of different forms.

*Orthopnea* signifies that dyspnea is more pronounced in the recumbent than in the upright posture. It has been suggested that orthopnea is due to diminished cerebral blood flow, but its absence in states of severe peripheral circulatory failure and in normal subjects when the venous return from the head is artificially impaired, makes such a hypothesis untenable. The available evidence suggests that the factors which tend to produce dyspnea in the recumbent position are as follows: (1) There is a shift in blood from the legs and abdomen into the lungs as the result of gravity. (2) The increased venous return in the recumbent posture tends to elevate the cardiac output by an amount variously estimated as 5 to 25 per cent. Such an increase, when occurring in a person with either mitral stenosis or left ventricular failure, will tend to produce an increased degree of pulmonary congestion (Chapter 14). (3) In the recumbent position the descent of the diaphragm is no longer aided by gravity. (4) As the result of these functional changes the vital capacity declines in the recumbent position, the degree of decline

being 5 to 10 per cent in the normal subject, and 10 to 30 per cent in the patient with congestive failure. Furthermore, in the case of the patient with congestive heart failure, there is a tendency toward increased volume of breathing as the result of the vagal stimulation consequent to increased degree of pulmonary congestion. Since both the numerator and denominator of the expression  $\frac{\text{ventilation}}{\text{vital capacity}}$  are affected in the direction of dyspnea, a further relatively slight change in each of them in the same direction will be attended by a relatively great increase in respiratory effort and by dyspnea.

*Paroxysmal cardiac dyspnea* is of two types: cardiac asthma and Cheyne-Stokes respiration. Both of these disturbances tend to occur during sleep, and hence are predominantly nocturnal.

The term "cardiac asthma" has the objection that it may be confused with bronchial asthma. On the other hand, the auscultatory phenomena resemble each other in the two conditions, and it has been shown recently that the prolonged expiration which is characteristically present in patients with bronchial asthma also occurs during attacks of cardiac asthma, and may be relieved within a few seconds by the intravenous administration of theophylline with ethylenediamine (aminophylline). This demonstration constitutes strong evidence for the existence of bronchospasm in cardiac as well as in bronchial asthma. The exact mechanism whereby the bronchospasm is brought about merits further investigation.

Cardiac asthma usually appears after the patient has been asleep for a time, occurs only in patients with lesions which affect the left side of the heart, and is characterized by seizures of dyspnea which force the patient to sit upright. It is commonly attended by "squeaks" and wheezes which resemble those of bronchial asthma, and which probably are due to spasm of the bronchial walls. In severe cases it may proceed to the alarming and often fatal complication, acute pulmonary edema, which occurs when extensive edema of the alveoli complicates congestion of the pulmonary capillaries. The attacks are often set off by various "trigger factors," including slipping down in bed, increase in blood volume and in the degree of pulmonary congestion as the result of nocturnal reabsorption of peripheral edema fluid, night-

mares, excessive warmth of the body, cough, distention of the abdominal viscera, etc. All of these trigger factors tend to act by causing increase in breathing, which augments inflow into the right side of the heart; this, in a patient with disproportionate dysfunction of the left side of the heart, aggravates pulmonary congestion, causing further respiratory stimulation, which further increases venous inflow and pulmonary congestion. Thus the vicious cycle proceeds until (rarely) it terminates fatally in an attack of pulmonary edema, or (commonly) it is broken by the elimination of the initiating trigger factor and by the assumption of the upright posture, which has the double effect of lowering the diaphragm and of causing blood to accumulate in the lower part of the body, thereby decreasing the amount of blood in the lungs.

Cheyne-Stokes respiration (periodic breathing) may occur during sleep or the dozing state in normal children and in healthy elderly subjects. Its appearance in disease is not limited to persons with cardiac disorders, for it may occur also in subjects with certain intracranial disorders such as acute cerebral hemorrhage, and may likewise develop during the course of certain intoxications such as uremia or morphinism. Its exact mechanism is unknown, but it seems to be intimately related to anoxic states as well as to various other conditions which depress the sensitivity of the respiratory center. In certain instances it is apparently caused by cyclic variations in blood pressure acting through the carotid sinus.

Cheyne-Stokes respiration is especially common in elderly patients with congestive failure, and tends to appear at the very onset of sleep when apnea occurs. After 20 seconds or more, breathing begins, the patient awakens, respiration becomes violent and, after the *crescendo* stage of a few seconds, becomes *diminuendo*, and finally terminates in apnea during which the patient again doses off into light sleep. The initial period of apnea which usually sets in at the onset of sleep is probably due to the sudden decrease in the sensitivity of the respiratory center. After a number of seconds of apnea the blood becomes rapidly deoxygenated, and the rapid conversion of oxyhemoglobin into the less acid reduced hemoglobin tends to make the blood more alkaline, and the period of apnea is further prolonged. When, as the result of carbon dioxide

accumulation, the respiration finally starts, the sudden reoxygenation of hemoglobin makes the blood more acid, and hence the breathing is *crescendo*. After reoxygenation is complete, the breathing diminishes and finally ceases as the result of carbon dioxide loss. Apparently, this rapid alternation between oxygen and carbon dioxide control, acting on a respiratory center alternately depressed and stimulated by the resting and sleeping states, or continuously depressed by drugs, poisons, or disease, is one factor in the production of the remarkable phenomenon of periodic breathing. However, this cannot be the sole factor, for Cheyne-Stokes respiration may occur in the absence of significant anoxia.

The general principles which have been stressed concerning the relationship between (1) the subjective phenomenon, dyspnea, (2) the objective but qualitative phenomenon, labored breathing, and (3) certain quantitative respiratory functions, vital capacity and ventilation, may be summarized conveniently as follows:

#### FACTORS IN THE PRODUCTION OF DYSPNEA

##### *I. Psychic:*

- A. *Disturbances of emotion:* May cause a sensation of dyspnea in the absence of labored breathing.
- B. *Disturbances of consciousness (Stupor, Coma):* May be associated with labored breathing in the absence of the sensation of dyspnea.

*II. Muscular:* Paralysis or extreme weakness of muscles may produce labored breathing and dyspnea by decreasing the maximum possible respiratory effort.

*III. Respiratory and Circulatory Disorders:* In these—the commonest causes of dyspnea—there is an increase in the actual respiratory effort, and a general parallelism exists between dyspnea and labored breathing.

A. *Obstruction to breathing* (e.g., bronchial asthma, mediastinal tumors, etc.): No necessary parallelism between dyspnea and  $\frac{\text{ventilation}}{\text{vital capacity}}$ .

B. *Disorders of the lungs:* Vital capacity usually decreased, ventilation usually increased.

1. Primary (e.g., emphysema, pneumonia, etc.). A general parallelism between
2. Secondary to cardiac disease (e.g., congestion edema). degree of dyspnea and ventilation

C. *Disturbances in the composition of the blood* (e.g., acidosis, anemia, anoxia, etc.): Unless primary or secondary pulmonary disorders coexist, dyspnea is usually slight and present only on effort, because only the numerator of the expression  $\frac{\text{ventilation}}{\text{vital capacity}}$  is abnormal.

#### EFFECT OF LABORED BREATHING

Regardless of its cause, labored breathing tends to be associated with an exaggeration of the normal changes in intrapleural pressure during the respiratory cycle. This exaggeration is particularly striking when there is respiratory obstruction, but also occurs when the lungs are abnormally rigid as the result of fibrosis or congestion, and when their elastic recoil is diminished as the result of emphysema. Under such circumstances the actual amount of work involved in the respiratory act is increased. Thus the oxygen consumption of the dyspneic individual is increased and the respiratory and circulatory systems are given an additional burden. It becomes clear that dyspnea, itself usually a result of cardiac or pulmonary disease, may induce a vicious cycle, the increased physical work associated with labored breathing tending to aggravate the underlying disease process. This conception explains why the administration of a drug such as morphine, which depresses breathing, may result at times in benefit which endures long after the immediate effect of the drug has disappeared. Under such circumstances the vicious circle has been abolished for a few hours, and this has resulted in improvement in the underlying disorder.

#### CLINICAL TYPES OF DYSPNEA IN RELATION TO DIFFERENTIAL DIAGNOSIS

The most important differential features of the more common causes of dyspnea may be summarized as follows:

1. **Dyspnea in Healthy Persons :** Only with exertion; degree of exertion required intimately related to body weight and to exercise habits.
2. **Cardiac :** Evidence of cardiac disease plus evidence of cardiac failure; prolongation of circulation time; orthopnea; nocturnal dyspnea.
3. **Pulmonary :** Cough often pronounced; pleural pain, cyanosis, or clubbing of the fingers frequently present; physical signs and radiologic evidence of pulmonary disease.
4. **Obstructive :** Wheezing, evidence of bronchial asthma, mediastinal tumor, etc.
5. **Hematogenous :** Clinical and chemical evidence of acidosis, anemia, or arterial anoxia; dyspnea absent or minimal at rest.
6. **Neurogenic :** (A) **PSYCHOGENIC:** Lack of evidence of above disorders; dyspnea closely related to emotional upsets; occasional deep sighing; hysterical panting, with excessive loss of carbon dioxide and tetany.  
 (B) **ORGANIC LESIONS:** Slow, stertorous breathing (increased intracranial pressure); rapid panting (hyperthermia); labored ineffective breathing (paralysis of respiratory muscles).

These several causes of dyspnea may now be considered in somewhat more detail.

In *normal persons* dyspnea does not occur at rest, and sets in upon exertion only when the exercise is strenuous or when adequate predisposing factors exist, including obesity, advanced age, and lack of "training." Furthermore, examination of the heart and lungs yields negative results. Dyspnea appearing only on effort should be considered as indicative of a pathologic state only when it is out of proportion to that normally occurring in individuals of similar age and weight, performing the same exercise.

Dyspnea of *cardiac origin* is recognized by the demonstration of the signs of cardiac disease (which are found by examination of the heart), and more particularly by the observation that the heart is enlarged, plus the demonstration of the signs of heart *failure* (which are found by examination of the patient as a whole). Aside

from the signs of failure of the right side of the heart (venous distention, increase in venous pressure, enlargement of the liver, dependent edema, proteinuria, and slight to moderate cyanosis) which are often absent, and which when present may bear little relationship to the severity of the dyspnea, it is of special importance to search for the signs of left-sided failure. These signs, which are closely correlated with the severity of dyspnea, consist of a story of progressive dyspnea on diminished effort, and, in many instances of recent attacks of nocturnal dyspnea, decreased vital capacity, rales at the lung bases (in most, but not in all instances), an essentially nonproductive, troublesome cough, prolongation of the pulmonary circulation time, and increased vascular shadows in the x-ray. In doubtful instances in which both cardiac and pulmonary disease are present, and one is in doubt as to which disorder is responsible for the dyspnea, the measurement of the circulation time may be of crucial importance.

Cardiac dyspnea may assume any of the various forms which have been mentioned. As a rule it consists of moderately rapid panting, the amount of air exchanged per breath not being increased. Since the vital capacity is consistently diminished, the degree of dyspnea and the severity of labored breathing are usually out of proportion to the degree of increase in the volume of air breathed per unit of time.

Except in cases of congenital cardiac disease, and instances of cardiac disorder secondary to chronic pulmonary fibrosis (*cor pulmonale*), cyanosis is apt to be slight, and clubbing of the fingers is usually absent in patients with cardiac dyspnea. When left-sided heart failure is complicated by acute edema of the lungs, or by pulmonary infarction, cyanosis becomes more marked.

*Dyspnea due to primary pulmonary disease* may or may not appear at rest, but always appears on exertion of sufficient severity. When present at rest the dyspnea may be severe, but more commonly is mild in proportion to the degree of cyanosis (pneumonia, miliary tuberculosis, and diffuse pulmonary carcinomatosis are exceptions in this respect). In proportion to the degree of lowering of vital capacity, pulmonary disease usually is associated with less dyspnea than cardiac disease. This is probably due to two

facts: (1) the vagal reflex is particularly sensitive to congestion; (2) the more chronic the pulmonary disorder, the less sensitive is the reflex.

Clubbed fingers are often present in patients with chronic pulmonary disease, but are absent when the disorder is of short duration. The chief points in the recognition of pulmonary dyspnea are the absence of evidence of cardiac disease and the demonstration by history, physical examination, and—more particularly—by the x-ray, of evidence of diseases of the lungs. It is noteworthy that one of the most common and serious of all pulmonary diseases—tuberculosis—rarely produces much dyspnea until it is widespread and far advanced.

*Obstructive dyspnea* occasionally may be brought about by disorders such as infections or tumors which cause excessive swelling of the pharynx, as well as unconscious states which allow the tongue to slip backward and obstruct the epiglottis; by disorders of the neck which compress the trachea (as Ludwig's angina, or angioneurotic edema); by disorders of the larynx (such as tetanic spasm, acute edema, carcinoma, or diphtheria); and by lesions obstructing the bronchi (bronchial asthma, mediastinal tumors, etc.). The cardinal features in the recognition of obstructive dyspnea are as follows: The respirations are noisy, being usually stertorous (like snoring) when the obstruction is above the level of the tracheal bifurcation, and wheezing when it is below this point. (The point of obstruction can be determined with fair accuracy by observation with the stethoscope as to where the noise is loudest.) In cases of bronchial asthma, coarse noises and musical squeaks are apt to be heard all over both lung fields. The degree of laboriousness of the breathing is out of all proportion to the normal, or only slightly augmented, respiratory rate. Cyanosis may be absent or extreme but is usually moderate to marked. Clubbing of the fingers is usually absent.

Acidotic patients with labored breathing usually present the characteristic picture of either diabetic coma or uremic stupor (Chapters 8 and 19). The characteristic odors of these disorders are usually present on the breath. The breathing is deep, somewhat sighing, and only slightly rapid (Kussmaul breathing). Since the vital capacity of the lungs is likely to be normal

and the cerebrum depressed, the subjective complaint of dyspnea may be entirely lacking. This statement also applies to the dyspnea of those subjects—such as dwellers at high altitudes—who have chronic arterial anoxia without cardiac or pulmonary disease. Cyanosis and clubbing of the fingers may be marked, but dyspnea at rest is usually absent. In anemic patients dyspnea is usually present on effort but does not appear at rest except when the anemia is very severe.

*In patients with disorders of the nervous system*, dyspnea may be of several types. Labored breathing may result from increased intracranial pressure (slow, stertorous breathing, or Cheyne-Stokes respiration), while rapid panting is often associated with the hyperthermia which may complicate various intracranial lesions, including tumor, hemorrhage, encephalitis, etc.

When, on the other hand, psychogenic disorders of the nervous system are responsible for dyspnea, the picture is quite different. In contrast to the absence of the complaint of dyspnea in the presence of obviously labored breathing which is observed in stuporous patients, the reverse is often true in the case of the patient with an emotional disorder. Commonly anxious, worried, and disturbed patients complain of a feeling of smothering or inability to get a deep breath. Inspection and spirographic tracings reveal normal respirations interrupted by an occasional deep sigh, the sensation of dyspnea appearing at this time and lasting only a few seconds. The diagnosis of this type of dyspnea, which is very common, is made on the characteristic history, observation of the occasional sigh, and the absence of evidence of organic disease.

Another type of psychogenic dyspnea is rarer but more dramatic. This is *hysterical hyperventilation* (the hyperventilation syndrome), which tends to occur in young women, especially those having severe neuroses or frank hysteria. The patient, who has no evidence of structural disease, has attacks which endure from a few minutes to many days. She usually complains of "nervousness and smothering." The dyspnea is no more marked during exertion than at rest, but is apt to be more striking when an observer is known by the patient to be present. The breathing is either unusually rapid or unduly deep. It usually is not particularly labored (the accessory respira-

tory muscles being brought into action in lesser degree than when corresponding tachypnea is due to organic disease). Talking does not tend to increase the degree of dyspnea. Cyanosis is conspicuously absent but manifestations of tetany, due to the alkalosis induced by carbon dioxide loss, and consisting of numbness in the fingers and circumoral regions, a drawing feeling in the hands and feet, muscular twitchings, and cramps, are often observed. Frequently, the patient complains only of "drawing," dizziness, weakness, or numbness, and unless the patient is observed during an attack, careful questioning may be needed in order to elucidate the fact that such symptoms are preceded by the respiratory disturbance.

*To summarize:* Dyspnea is a subjective phenomenon, the cortical reflection of the same stimuli which, acting on lower centers, produce labored breathing. In the absence of impairment of consciousness and of emotional disturbances, a close parallelism usually exists between the degree of dyspnea and the degree to which breathing is labored. When there is no obstruction to the airways, the severity of dyspnea tends to parallel the closeness with which the actual respiratory minute volume approaches the maximum possible respiratory minute volume. Hence, any condition which increases the volume of air breathed, or decreases the amount which can be breathed (i.e., the vital capacity), tends to cause dyspnea which is particularly severe when both of these functions are affected. The

most important causes of dyspnea are, therefore, diseases of the heart and lungs, and disorders which cause obstruction to breathing. Disorders which stimulate breathing but do not alter the lungs (either directly or indirectly, as the result of congestion and edema) are less important causes of dyspnea. In the differential diagnosis of dyspnea one first searches for evidence of cardiac, pulmonary, and obstructive disorders, and then considers conditions which alter the composition of the blood, and disturbances of the nervous system.

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# 10

## Cough and Hemoptysis

Paul B. Beeson

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### COUGH

**Mechanism.** Cough is a reflex act which occurs in response to irritation of the surface of the respiratory tract. The stimulus may arise anywhere between the pharynx and the secondary branches of the bronchi. The afferent part of the reflex arc is in the vagus nerve, while the efferent part includes the various nerves supplying the muscles of respiration.

The act of coughing has three phases: inspiratory, compressive, and expulsive. A cough is nearly always preceded by indrawing of air; this fills the lungs with a charge to be forcibly expressed. The compressive phase is a brief period in which the motions of expiration are begun, but with the glottis closed. This causes a building up of pressure within the thoracic cavity, so that when the glottis suddenly opens and the expulsive phase begins, air rushes at high speed through the respiratory passages to the outside. The velocity of air in the larynx is very great, whereas the speed is much less in the peripheral portions of the bronchial tree.

In the compressive and expulsive phases of coughing, the thorax is elongated and fixed by the intercostal muscles. Contraction of abdominal muscles also elongates the thorax and, in addition, drives the diaphragm up into it like a piston. These acts produce a concentric pres-

sure within the thorax, the only outlet for which is the air passages. It is thought that the diaphragm does not function as an inert membrane during coughing, but rather that it acts as the antagonist, serving to brake and modify the forceful expiratory motion.

**Drainage of Air Passages.** Cough is only one of the mechanisms which act together to drain the air passages. Several other factors are of importance: (1) During ordinary respiration there is a rhythmic change in the dimensions of the bronchi. In inspiration they become elongated and increased in diameter. During expiration they become shorter and narrower. Because of this the velocity of air movement is greater during expiration than during inspiration. The effect of this difference in air velocity during ordinary respiration is therefore to waft particulate matter out of the lungs. (2) The motion of cilia of the respiratory mucosa tends to propel secretions and adherent particles out of the respiratory tree. In the living dog, for instance, it has been shown that ciliary action is capable of moving a drop of oil along the surface of a bronchus at a rate of 1 cm. in 80 seconds. (3) Peristaltic movements of the bronchi have been noted during fluoroscopic "Lipiodol" studies and also in direct observations with the bronchoscope. Whether such movement actually assists in drainage of the lungs cannot be stated with certainty. (4) "*Tussive squeeze*" is a term used by Chevalier Jackson to describe the compression of peripheral pulmonary tissue which occurs during expiration, and which is exaggerated during cough. The effectiveness of this process can be observed during bronchoscopy; it seems to be an important means of expressing material from the smaller bronchi. Jackson compares it to the squeezing of a sponge. It is most effective in the peripheral parts of the lungs, where cough is least effective.

Natural mechanisms for drainage of the air passages include, then, a group of processes, which complement one another. The peripheral areas of the lungs are drained by air currents,

ciliary action, the "tussive squeeze," and possibly also by peristalsis. These processes bring material into the larger bronchi, where the blast of air generated by coughing is efficient enough to carry it out of the respiratory tract.

**Harmful Effects of Cough.** Although cough is ordinarily an important factor in pulmonary drainage, it is not an unmixed blessing: (1) Instead of helping to expel matter from the smaller bronchi, cough may have an in-driving action, as has been observed during fluoroscopy. After one or two coughs, "Lipiodol" which had previously been in medium-sized bronchi has been found to have moved out into what appears to be an alveolar distribution. The mechanism by which this occurs may be an intense constriction of the bronchi during coughing, tending to force the "Lipiodol" peripherally as well as centrally. Or it may be due to unequal filling of different areas with air during inspiration, so that in the succeeding expulsive phase the air emerging from a neighboring bronchus would force "Lipiodol" peripherally. Animal experiments indicate that the in-driving action of cough is more likely to occur when the material in the bronchi is of low viscosity than when it is thick and tenacious. Here is a possible explanation of the fact that pulmonary hemorrhage often leads to wide dissemination of tuberculosis. (2) Cough may spread infection from one part of a lung to another in a different way. Fluoroscopic studies in human beings have shown that collections of "Lipiodol" in abscess cavities can move, in the course of a few coughs, not only to different parts of the bronchial tree of the same side but also into the opposite lung. This is undoubtedly a way in which infection spreads throughout the lungs. (3) The paranasal sinuses may be seeded with infected material from the lungs during cough. Roentgenologists have noted transfer of "Lipiodol" from the bronchial tree into the paranasal sinuses after coughing. Thus it may be that in the frequently observed combination of bronchial and sinus infection, the infection in the sinuses is sometimes secondary to that in the lungs. (4) Both lungs have a common pathway of exit; yet, were motion of one side of the chest limited by pain, the blast of air from the other side could have much greater force, thus impeding drainage of the affected lung. (5) There is clinical evidence that laryngeal tuberculosis is caused in part by the trauma of frequent cough-

ing, and that its incidence can be reduced by training patients with tuberculosis to refrain from coughing except when sputum can be raised. (6) The mechanical disturbance associated with cough may rupture a lung abscess or pleural adhesion, dislodge a clot and start fresh hemorrhage, or interfere with the mechanical rest which is helpful in the healing of tuberculosis. (7) Cough interferes with sleep and places an additional burden on the heart in patients with cardiac decompensation. In certain patients with congestive failure the control of cough is the most useful therapeutic measure which can be instituted.

### COUGH AS A SYMPTOM

Cough is a very common symptom, though not always a prominent one. For example, in typhoid fever, while cough is nearly always present early in the disease, other discomforts such as headache, malaise, abdominal pain, and diarrhea occupy the patient's attention. Even in pneumonia the patient may be so distressed by pleuritic pain, headache, and fever that he does not complain of his cough. There are, however, some common diseases in which cough is usually the outstanding symptom:

**Acute Bronchitis.** At the onset the cough may be "dry" and nonproductive, but by the end of one or two days a mucoid sputum begins to appear; this later takes on a purulent character. Pleuritic pain is not characteristic of bronchitis, although the severe coughing often causes soreness in the region of the lower costal margins as a result of the strain on the attachments of the diaphragm and abdominal muscles. Also it is not unusual for the patient to complain of a burning or raw sensation beneath the sternum. Chest x-ray shows no abnormality. There may be scattered moist rales.

**Chronic Bronchitis.** Cough and expectoration are usually the only symptoms. These are apt to be particularly troublesome in the morning, because the change in position and deeper breathing cause exudate to flow into the larger bronchi; this stimulates the cough reflex.

**Bronchiectasis.** As in chronic bronchitis, cough and expectoration are the principal symptoms. Here also they are likely to be most severe in the morning. The volume of sputum is sometimes very large; as much as a quart may be produced in a single day. The patient's breath

and sputum usually have an offensive odor. The sputum, when allowed to stand in a glass vessel, settles into three layers: an upper froth, a central clear liquid, and a sediment of thick yellowish or greenish purulent particles. Physical examination usually reveals moist and dry rales throughout the lower lung fields. Chest x-ray may show no abnormality, but bronchogram with iodized oil gives a positive diagnosis. The finding of clubbing of the fingers in a patient with chronic cough should suggest this diagnosis. These patients are subject to recurrent attacks of pneumonia, in the same areas of the lung.

**Pulmonary Tuberculosis.** This disease is commonest in young adults, but it occurs with sufficient frequency in older persons to merit consideration as a cause of cough at any age. In young people it is frequently accompanied by hemoptysis or by other manifestations of infection: fever, night sweats, and weight loss. In old people cough may be the only manifestation for months or even years. Physical signs may be detected in the upper parts of the lungs, but are usually absent in very early cases. Chest x-ray is the best diagnostic measure. Positive diagnosis depends on the finding of tubercle bacilli in sputum or gastric washings. A negative tuberculin reaction helps to exclude the diagnosis.

**Bronchogenic Carcinoma.** This disease is commoner in males who are past middle age. Cough is often the first symptom. Hemoptysis may be associated. Pain usually signifies invasion of neighboring structures. There may be no physical signs. Chest x-ray may be negative in the early stages, but since bronchial obstruction predisposes to the development of pneumonitis or atelectasis, the signs of these conditions may be found. It is often possible to observe the tumor through the bronchoscope. Bronchogram with iodized oil may also be very helpful. Biopsy of tissue accessible through the bronchoscope or by needle aspiration provides the complete diagnosis.

**Pulmonary Infarction.** Clinical experience provides ample evidence that pulmonary infarcts may cause no other sign or symptom than cough. Hemoptysis, pleuritic pain, fever, tachycardia, and icterus, when present, make diagnosis easier, but any or all of those may be absent. X-ray of the chest will often show a localized opacity near the periphery of a lung field, usually in the lower half. A time interval of about 18

hours after the lodging of an embolus is required before x-ray signs can be detected.

**Cardiac Decompensation.** When the heart fails gradually, cough is frequently a prominent symptom. It is usually nonproductive and may be troublesome, interfering with sleep. It seems to be due to congestion of the pulmonary blood vessels, and can be present when there is no clinical or roentgenologic evidence of pulmonary edema. The cough often subsides following such therapeutic measures as digitalization, rest, and mercurial diuresis.

**Aortic Aneurysm.** This disease is commoner in males and in the Negro race. It seldom occurs before the age of 30. A brassy, nonproductive cough is often the first symptom and is presumably caused by pressure against a bronchus or the trachea. The "brassy" character is generally ascribed to recurrent laryngeal nerve paralysis. Physical signs of special significance are tracheal tug and widening of the supraventricular area of dullness. Chest x-ray and fluoroscopy are particularly helpful.

**Psychogenic Cough.** Secondary neurotic uses of cough are not uncommon; these are encountered most frequently in patients with cough of organic origin which is used secondarily for the purpose of giving expression to repressed impulses, often of hostile nature. Another common type, of stubborn quality, is the nervous cough which is really a tic, comparable to eye winking or facial grimaces or noises in the throat.

## HEMOPTYSIS

Bleeding from the lungs is an important and fairly common medical problem. It is, of course, important to ascertain that blood is actually coming from the pulmonary tree, not from the gastrointestinal tract or the nasopharynx. Blood which comes from the lungs is often bright red and frothy in appearance, whereas that from the stomach may be dark red, brown, or black, and may be mixed with particles of food. Vomiting of blood is usually preceded by a feeling of nausea and commonly accompanied by retching, whereas hemorrhage from the lung may begin without antecedent symptoms, and usually is accompanied either by coughing or by clearing of the throat. Not infrequently patients with bleeding in the lung experience a vague sensation which enables them to tell the approximate location of the hemorrhage.

**Hemoptysis Associated with Hard Coughing.**

Very commonly, persons who have a hard, forceful cough will produce sputum which is blood-streaked. This is a result of trauma to the air passages from the force of the coughing and is of little clinical significance. This type of hemoptysis usually can be identified by the history and by inspection of the sputum, noting that the blood is streaked on the surface, not intimately mixed with it.

**Pneumonia.** The sputum in bacterial pneumonia nearly always contains blood; only rarely is this the case with the viral pneumonias. In pneumococcal pneumonia the sputum may be pink or red, but more commonly, because of bacterial growth, the color is "rusty" or "prune juice." In staphylococcal pneumonia the sputum may be "rusty" or it may be a bright cherry red. In Friedländer bacillus pneumonia the sputum is characteristically bloody and tenacious, varying in color from dark brown to bright red. In pneumonia of any etiology the sputum seldom resembles pure blood; nearly always it is a mixture of mucopurulent material with blood.

**Pulmonary Infarction.** Clinicians are becoming more and more aware of the frequency and seriousness of pulmonary infarction due to embolism in the pulmonary vessels. This is the commonest cause of hemoptysis which occurs in the course of a nontuberculous illness in a hospital patient. Emboli come most frequently from thromboses in the deep veins of the calves but may originate in the pelvic veins or the right side of the heart. Occlusion of a pulmonary artery by an embolus usually is followed by turgescence of the capillaries in the area of lung supplied by that artery. The influx of blood is by way of capillary anastomoses from neighboring areas and is perhaps intensified by reflex spasm of the veins draining the area. This impaired circulation leads to necrosis, and entry of blood cells and edema fluid into the alveoli of the part; it is this material which appears as sputum. The excellent studies of Hampton and Castleman have shown that the incidence of pulmonary infarction following embolism is approximately 90 per cent in patients with heart disease, contrasted with an incidence of about 60 per cent in other diseases. The higher incidence in cardiac patients probably is due to the already existing congestion and slow blood flow in the pulmonary circuit.

**Bronchiectasis.** It is estimated that hemoptysis occurs in 50 per cent of patients with bronchiectasis, and in young people this is one of the most frequent causes of the symptom. Erosion of the inflamed bronchial mucous membrane, by infection or the trauma of coughing, causes bleeding. Diagnosis in this type of hemoptysis is usually not difficult, in view of the history of chronic productive cough and positive findings on the bronchogram. Often, however, the bleeding point is located too far in the periphery for identification by the bronchoscopist.

**Pulmonary Tuberculosis.** Small hemorrhages may occur early in the exudative phase of tuberculosis, as a result of direct erosion of vessels. In chronic ulcerative tuberculosis, bleeding occurs from incompletely obliterated pulmonary vessels which run through or along the walls of cavities. In some cases the source of bleeding is an aneurysmal dilatation, and this may bleed profusely.

Although hemorrhage in pulmonary tuberculosis is seldom immediately fatal, it may have serious effects. The plugging of a large bronchus with blood may cause atelectasis. Of even greater seriousness is the widespread dissemination of the tuberculous infection which may occur. Blood from a tuberculous cavity may be heavily contaminated with tubercle bacilli, and, as discussed previously, because of its fluidity it may be widely distributed throughout the lungs by coughing.

**Pulmonary Neoplasms.** Adenomas of the bronchi nearly always cause hemoptysis which is likely to be profuse. In bronchogenic carcinoma, the symptom is present in 25 to 50 per cent of cases. The source of bleeding is erosion of the surface of the tumor, within the lumen of the bronchus.

**Mitral Stenosis.** Obstruction to the emptying of the left atrium very frequently causes blood spitting; some authors place mitral stenosis second only to tuberculosis as a cause of hemoptysis in young people. Most writers have attributed the bleeding to increased pulmonary venous pressure with diapedesis into the alveoli. Ferguson, Kobilak, and Deitrick, however, suggested that the bleeding in mitral stenosis is due in many cases to the rupture of submucous varicosities in the bronchi. By examination of lungs removed at autopsy they proved the existence of venous anastomoses between the

pulmonary and bronchial veins. They found, furthermore, that in patients with mitral stenosis these anastomoses were markedly increased in size, resembling small varicose veins. It was their opinion that the increased pressure in the pulmonary veins in mitral stenosis caused the dilatation, and permitted some blood to drain from the pulmonary into the bronchial venous system. This hypothesis is attractive as an explanation of the cause of the large hemorrhages which sometimes occur in mitral stenosis.

**Other Causes.** The diseases mentioned previously are the principal causes of pulmonary hemorrhage, although various others occasionally may be responsible. In aneurysm of the aorta there may be bleeding through an eroded bronchus. Rarely, hemoptysis occurs in patients with arterial hypertension, presumably due to rupture

of a submucous artery. Abscess in the lung may cause bleeding, as may the various purpuric states.

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## Section 4—Disturbances in Circulation

# 11

## Palpitation

William H. Resnik

### Pathogenesis of Palpitation

#### Important Causes of Palpitation

Palpitation Due to Disorders of the Mechanism of the Heart Beat

Palpitation Dependent on Presence of Some Organic or Functional Disturbance Originating Outside the Circulatory System

Palpitation Due to Functional Disorders of Circulatory System

Onset of Congestive Failure

Palpitation is to be defined as the consciousness of the beating of the heart. From the standpoint of diagnosis, it is not usually a very important symptom. Excepting certain cardiac arrhythmias, palpitation is not pathognomonic of any particular group of disorders, and even when it occurs as a more or less prominent complaint, the diagnosis of the underlying malady is made largely on the basis of other associated symptoms and data, rather than by an analysis of the palpitation alone. Nevertheless, palpitation frequently constitutes a symptom of considerable importance in the minds of patients. The clear association of this symptom with the function of the heart, and the fear engendered by the suspicion that heart disease may be present, account for the apprehension frequently inspired by the consciousness of the heart beat. This anxiety is all the more pronounced in patients who know or who have been told that they have heart disease, and to them palpitation may be an omen of impending disaster.

In the following paragraphs a number of conditions will be discussed primarily from the standpoint of palpitation. It must not be inferred, however, that in all these disorders palpitation is always a symptom of great magnitude, even from the patient's standpoint. Palpitation may be absent without affecting the ultimate diagnosis; but in the various conditions discussed below, palpitation *may* be the chief source of the patient's discomfort, and the outstanding complaint. Palpitation may be expressed by the patient in various terms, such as "pound-

ing," "fluttering," "flopping," "skipping," and in most cases it will be obvious that the complaint is being applied to a sensation denoting a disturbance of the heart beat.

### PATHOGENESIS OF PALPITATION

Under ordinary circumstances the rhythmic heart beat is imperceptible to the healthy individual of average or placid temperament. Palpitation may be experienced by normal persons who have engaged in a strenuous physical effort, or who have been strongly aroused emotionally. This type of palpitation is physiologic and represents the normal awareness of an overactive heart—that is to say, a heart that is beating at a rapid rate and at the same time expels more than the usual amount of blood with each beat. Since palpitation accompanies physiologic overactivity of the heart as well as certain pathologic forms of overactivity, such as is seen in severe anemia or thyrotoxicosis, it is commonly assumed that the overactivity, *per se*, is responsible for the symptom. However, overactivity of the heart consists of two components—increased rate and increased output per beat—and some idea of the relative importance of each can be gained by inquiry into those conditions in which the two functions are altered in opposite directions. The various forms of paroxysmal tachycardia, most cases of untreated auricular fibrillation, and some instances of flutter are characterized by a conspicuously increased heart rate and a notably diminished output per beat; hence the palpitation commonly experienced in these disorders must be attributed primarily to the tachycardia. In auricular fibrillation, and in some cases of flutter, the irregularity of the ventricular beat may be an additional factor that contributes to the palpitation, but even in these conditions the severity of the palpitation diminishes practically to the vanish-

ing point as the ventricular rate is lowered to normal levels by the action of digitalis. On the other hand, complete heart block, in the absence of congestive failure, is characterized by a slow heart rate and considerably increased output per beat; in this condition palpitation is conspicuous by its rarity or absence. These observations would seem to emphasize the importance of increased heart rate as compared with increased output per beat in causing palpitation, although it is probable that, given an increased heart rate, palpitation will be enhanced by an accompanying increased stroke volume.

**"The premature beat** is the outstanding arrhythmia that is likely to cause palpitation in the presence of a normal heart rate, but even this exception to the rule—that the rapidity of the heart rate is the main determining factor in causing palpitation—bears inspection. The consciousness in normal individuals of the very first beat, and often of the last one, of a paroxysm of tachycardia is indicative of the fact that many persons are normally aware of sudden and striking alterations in the heart rate. In fact, it is the history of the sudden onset and offset of a paroxysm that is the sole basis for the clinical recognition of the condition when it is not under immediate observation. There is as yet no general acceptance of the basic mechanisms underlying either the premature beats or the paroxysmal tachycardias, but from an electrocardiographic standpoint the latter behave like a continuous series of premature beats. If the normal individual can be made conscious, as he often is, of the first beat of an abnormal rhythm characterized by its rapid rate, it is not illogical to invoke the same explanation for the consciousness of a single isolated beat of the same type as the basis for the common perception of the extrasystole. At a regular ventricular rate of 70 per minute and a systole of 0.3 second's duration, a premature beat in the early part of diastole would give the equivalent of a momentary heart rate of 140 to 180.

\* It is possible that palpitation may depend on the phenomenon known in physiology as the summation of inadequate stimuli. A stimulus of subthreshold value, incapable of setting up an impulse in a nerve, can be built up to the necessary level by a second stimulus or a series of subthreshold stimuli applied at short intervals. Similarly, the heart, beating at a normal rate in

a normal individual, creates a stimulus in the afferent nerves that is of a subthreshold value either for the propagation of the impulse through the nerves, or for the stimulation of the higher centers to which the nerves lead. A second stimulus (extrasystole) or a series of stimuli (tachycardia) developing at short intervals may, by their combined effect, exceed the threshold value and hence be felt in consciousness. The heart, with a larger output per beat, may give rise to a greater than normal stimulus, though still below threshold value; but the total effect of similar but rapidly repeated stimuli would be responsible for the more intense palpitation that is felt in exercise, as compared with that felt in other conditions characterized by a similarly elevated heart rate, but also by a diminished output per beat. Whether this mechanism, the summation of inadequate stimuli, or some other is responsible for palpitation, once aroused, it seems to persist for a brief period after the effective stimulus has ceased to operate. It is common for the patient with extrasystoles to complain of the pounding sensation imparted by the large beat succeeding the pause. This phenomenon is commonly attributed to the unusually large output of the particular beat occasioned by the unusually long period of diastolic filling. This explanation certainly cannot represent the entire or even the chief reason for the thump following the extrasystolic pause. In heart block with intermittences, equally long or even longer periods of diastolic filling are rarely if ever followed by a thumping sensation, although the output of the heart following the pause can be assumed to be of the same order as the one that does cause the pounding sensation in the extrasystolic arrhythmia. In other words, the large beats in heart block are practically always of subthreshold intensity, while those in the extrasystolic irregularity are often of threshold value. One can assume, in the latter case, that the mechanism aroused by the premature contraction persists for a brief interval, permitting a heart beat that ordinarily would be below the level of consciousness to remain above the threshold level. The consciousness of the heart's action excited by the premature beat may be manifested in another interesting fashion. The patient is often conscious of the pause that follows the ectopic beat. Taking again the example of a ventricular rate of 70, a systolic duration of

0.3 second, and a premature contraction at the earliest part of diastole, a fully compensatory pause would be of 1.37 seconds' duration, equivalent to a regular ventricular rate of 44, such as might be seen in sinus bradycardia or heart block. Here again the mere duration of the pause cannot satisfactorily explain the fact that it is so frequently felt following the premature beat, since equally long, or longer, pauses are generally unnoticed in the other conditions mentioned. Similarly, the consciousness of the sudden termination of a paroxysm of tachycardia must be conditioned by the presence of the preceding tachycardia; when carotid sinus stimulation brings about a sudden and marked slowing of the ventricular rate from initial levels of 60 to 80, the individual is unaware of the change in the heart rate except indirectly through appearance of the dizziness and faintness.

In the above discussion we have assumed that palpitation—consciousness of the beating of the heart—is due to the transmission of threshold stimuli (or the summation of subthreshold stimuli) along the afferent nerves. We have left unanswered the question: What particular activity of cardiac function is responsible for the afferent stimulus that gives rise to palpitation? We have purposely limited these remarks to an examination of the obvious features of heart rate and output per beat. One hypothesis suggested as the cause of palpitation associated with premature beats is also applicable in the explanation for the importance of increased heart rate as a cause of palpitation. This hypothesis involves consideration of the observations concerning the relationship between the ventricular volume curve, the position of the atrioventricular valves, and the intensity of the first heart sound. These relationships are illustrated diagrammatically by figure 19. It can be seen that, when the duration of diastole is very short (and the atrioventricular gradient is normal or increased), the succeeding systole occurs at a time when the atrioventricular valves are widely patent and pressed against the ventricular walls, and, hence, that the degree of movement of the valves at the onset of systole is great and the first sound is loud. When, on the other hand, the duration of diastole is long, the valves tend to float up into a position of semiclosure during the latter part of diastole and the first sound is faint. Similarly, when the atrioventricu-

lar pressure gradient is small, either as the result of a low filling pressure or of the presence of residual blood in the ventricles, the valves fail to be pressed against the ventricular walls, and closure of the valves by systole takes place when

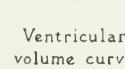
Circulatory State	Normal	Early Ventricular Premature Beat	Late Ventricular Premature Beat
Auriculoventricular pressure. Gradient just prior to ventricular systole	Medium	High	Low
Ventricular volume curve			
Position of A-V valves at onset of ventricular systole			
Intensity of first heart sound	Moderate	Loud	Faint
Palpitation	Absent	Present	Absent

FIG. 19. In the ventricular volume curves the dotted lines represent systole and the solid lines diastole. In the case of the normal state, the time elapsing between the auricular systole (a) and the succeeding ventricular systole is sufficiently long for the pressures in the two chambers to begin to equalize, and the valves have assumed the midposition. When the premature beat (arrow) occurs early in diastole, the valves are widely open and the resulting first sound is loud and accompanied by palpitation. When the premature beat (arrow) occurs later in diastole, the valves are partially closed; neither intensification of the sound nor palpitation occurs. (Further consideration of the ventricular volume curve in relation to the heart sounds will be found in Chapter 235.)

they are already in a position of semiclosure. Thus palpitation may conceivably be a sensation accompanying an unusually rapid excursion and tensing of the atrioventricular valves. These considerations may suffice to explain some of the otherwise baffling questions concerning the presence of palpitation, such as its rarity in congestive heart failure despite moderate tachycardia (diminished atrioventricular pressure gradient as the result of increased residual blood in the ventricle) and its usual absence in peripheral circulatory failure despite marked tachycardia (diminished atrioventricular gradient as a result of diminished venous return). In paroxysmal tachycardia the circumstances are more complicated, depending on the summation of a number of variable factors: the diminished atrioventricular pressure gradient in the early stages, which becomes exaggerated in the pro-

longed bouts as myocardial failure supervenes; the shortening of diastole and shortening of the P-R interval, which result in a systolic contraction of the ventricle when the atrioventricular valves are wide open; and the diminution of this effect on development of heart failure when the ventricles empty incompletely, so that the A-V valves are in a position of partial closure at the moment of ventricular contraction. Actually, there are available no carefully controlled studies undertaken to investigate the question of palpitation, and further speculation regarding the factors involved in the causation of this symptom would be fruitless at the present time.

In all instances the severity of the palpitation will vary with the individual's threshold of sensitivity to sensory stimuli. It is a matter of common experience that an identical stimulus will be registered with different degrees of intensity on the consciousness of various persons, depending on differences of temperament; and of the same person, depending on his emotional state and other influences known to affect the acuity of perception. In general, then, it may be concluded that palpitation is determined by the rate and, to a lesser extent, by the force, regularity, size, and efficiency of the ventricles; and the actual level of the heart rate at which palpitation will appear and the intensity with which it is felt will be governed, in addition, by the sensitivity of the individual.

A symptom somewhat allied and often confused by the patient with palpitation is the perception of the throbbing of the arteries of the neck. This may occur under the same conditions that produce palpitation, and rarely may be the complaint of the patient when actual palpitation is absent. It may also occur when the pulse pressure is elevated.

### IMPORTANT CAUSES OF PALPITATION

Since palpitation may be caused by any condition that raises the heart rate sufficiently, it is impracticable to enumerate all the circumstances under which this symptom may be felt. It will be more useful to outline those disorders in which palpitation is the predominant symptom, or in which the appearance of palpitation may serve to indicate the presence of some condition, otherwise more or less obscure, in

which an increased heart rate is a common phenomenon.

**1. Palpitation Due to Disorders of the Mechanism of the Heart Beat (EXTRASYSTOLES).** The symptoms are fairly consistent, and in most cases the diagnosis will be suggested by the patient's story. The actual premature contraction is often described as a "flopping" or as if "the heart turns over"; the pause following the premature contraction is felt as an actual cessation of the heart beat, in contrast to the complete unconsciousness of the pause when the heart beats normally or at a slow rate, and the patient will often magnify the duration of the interval and sometimes express apprehension as to whether the heart will actually resume its beat; the first ventricular contraction succeeding the pause is felt as an unusually vigorous beat and will be described as "pounding" or "thudding." Any one, or all three, of these different symptoms initiated by the premature contraction may be experienced by the patient. Usually the identification of the extrasystole as the cause of the palpitation is a simple matter. When numerous extrasystoles are present, differentiation from auricular fibrillation can be made by any procedure that will bring about a definite increase in the ventricular rate; at increasingly rapid heart rates, the extrasystoles diminish in frequency and then disappear, whereas the irregularity of auricular fibrillation increases. Heart block, with dropped beats, is the only other common arrhythmia with which the premature contraction is likely to be confused; here, simple auscultation will reveal the absence of the premature beat prior to the pause.

**X PAROXYSMAL TACHYCARDIA.** There are various types of paroxysmal tachycardia, depending on the particular region of the heart in which the abnormal rhythm originates. They are all characterized by an absolutely sudden onset and equally sudden offset; the rate is rapid, usually between 160 and 200, in flutter sometimes lying between 130 and 160; and the regularity of the heart's action depends on the particular type of paroxysmal tachycardia. The symptoms during the attack are those that accompany any pronounced tachycardia, whatever the origin. If the physician is present during the attack, the response to carotid sinus stimulation and observations regarding the constancy of the heart rate usually will suffice to determine whether the

patient is suffering from a simple tachycardia or one of the various forms of paroxysmal tachycardia. Electrocardiographic examination, when this is possible during the attack, will usually be decisive. Assuming, however, that the patient complains of attacks of palpitation, and at the time of the examination no abnormality of the heart can be detected, the diagnosis of paroxysmal tachycardia must rest on securing from the patient a history of abrupt onset and offset of the attack. (See Chapter 235.)

In many cases of rapid heart action, it is difficult or impossible to determine with certainty, from the patient's story, whether the attack has started and ended abruptly, and whether tachycardia or anxiety has been primary.

**AURICULAR FIBRILLATION.** The establishment of this irregularity as the cause of palpitation is usually a simple matter. In the untreated case the rate is ordinarily 120, or higher, and the rhythm characteristically totally irregular. Moreover, the absolute irregularity persists as the rate increases—an important diagnostic feature in distinguishing this arrhythmia from all others.

**AURICULAR FLUTTER.** When the rhythm is regular and the ventricular rate is fixed at a rate lying between 125 and 180, remaining unchanged regardless of rest, exercise, or emotional strain, and when such a constant rate is maintained over a period of time, the presence of auricular flutter as the basis for the accompanying palpitation is a practical certainty.

In all these instances of palpitation caused by disturbances of the mechanism of the heart, the history and routine physical examination should be supplemented by electrocardiographic study. In some cases, as in patients who suffer from paroxysmal tachycardia but who are first seen in an interval between attacks, the electrocardiogram will show little or nothing that is of decisive value in determining whether or not an actual paroxysm has taken place in the past. In rare instances, the characteristic tracing of the Wolff-Parkinson-White syndrome will be revealed as the cause for previous attacks of palpitation whose nature has been obscure. In other cases, the differentiation between frequent extrasystoles, auricular fibrillation, and auricular flutter, with varying degrees of heart block, will be established with certainty when the history and routine physical examination have been

inconclusive. In cases where doubt exists as to the nature of a regular tachycardia, the electrocardiogram, if taken during the attack, as well as observations on the effect of carotid sinus pressure, will make the differentiation possible.

**2. Palpitation Dependent on Presence of Some Organic or Functional Disturbance Originating Outside the Circulatory System.** Tachycardia and palpitation accompany such a wide variety of disorders that enumeration and discussion of all would be impracticable and obviously futile. Only the more important ones, particularly those that may not be readily recognized, will be mentioned.

**II THYROTOXICOSIS.** In its fully developed form, thyrotoxicosis will usually be evident, and offers little difficulty in the way of diagnosis. It is the lesser grades, particularly those that are complicated by the presence of myocardial failure, that are likely to be overlooked. The suspicion that thyrotoxicosis is present may be aroused by the detection of any one of its characteristic features, and confirmation of the diagnosis will be obtained by the finding of an elevated metabolic rate. However, it is to be borne in mind that an elevated basal metabolic rate usually is present in myocardial failure, even when thyrotoxicosis is absent. Hence, when congestive failure of even mild degree is present, a moderate increase in the basal metabolic rate, unassociated with any of the other characteristic manifestations of thyroid overactivity, cannot be considered unequivocal proof of the presence of hyperthyroidism. In doubtful cases, observations of the circulation time and of the effect of administration of iodine or of a thio-uracil derivative may be of value.

**II ANEMIA.** When mild, anemia may cause palpitation during exertion; when severe, it causes palpitation at rest. In some patients the coloring of the skin may not reveal the cause of the symptom, but appropriate studies of the blood will clarify the situation.

**ACUTE HEMORRHAGE.** Acute hemorrhage, most commonly in the gastrointestinal tract, may be responsible for the sudden development of weakness, faintness, and palpitation when the cause is not immediately apparent.

**FEVER.** Palpitation may be present in acute infections, particularly in the early stages; but here the symptom is merely an insignificant phenomenon in the midst of other obviously

more important ones. Palpitation may be one of the more prominent symptoms in an individual suffering from one of the chronic and sometimes more obscure febrile illnesses, such as incipient tuberculosis, chronic brucellosis, subacute bacterial endocarditis, or acute rheumatic fever with carditis and relatively few or no joint manifestations. Carditis in acute rheumatic fever, and subacute bacterial endocarditis, cannot, of course, be considered causes of palpitation originating outside the heart. They are considered in this group because the presenting symptoms, including palpitation, are often only those of an infection without localizing symptoms that direct suspicion to the heart. The problem is to determine that the cause of the palpitation is an infectious illness, and to carry out the usual procedures to reveal the type of infection.

**HYPOLYCEMIA.** This constitutes one of the most common causes of palpitation, probably as the result of release of epinephrine. Palpitation, weakness, hunger, faintness, increased perspiration, and tremulousness constitute the main features of the full-blown picture of the hypoglycemic reaction. Confirmation of the diagnosis is obtained by appropriate blood sugar estimations and by prompt relief of all symptoms on the administration of glucose in one form or another. Palpitation may be the outstanding symptom in less typical cases in which several of the usual manifestations are absent. The clue to the correct diagnosis will usually come from the elicitation of a history revealing the characteristic appearance of symptoms several hours after the preceding meal, particularly when the influence of other causes of palpitation such as exercise or emotional strain can be eliminated. In doubtful cases the reproduction of the exact symptom complex of the spontaneous attacks by the injection of insulin may be a valuable diagnostic aid (Chapter 7).

**AEROPHAGIA.** Many patients who complain of "gas" and belching also complain of palpitation which appears to be related to the distended stomach, accompanied in most instances by a lowered threshold of perception. This type of palpitation is readily recognized by the history of relief from eructation.

**TUMORS OF ADRENAL MEDULLA (PHEOCHROMOCYTOMAS).** Such tumors may give rise to recurrent attacks whose symptoms, including

paroxysms of hypertension and palpitation, are identical with those seen following the injection of epinephrine. This type of tumor is rare and is mentioned solely because cure may be effected by surgical removal.

**DRUGS.** The relationship between the development of palpitation and the use of tobacco, coffee, tea, alcohol, epinephrine, ephedrine, aminophylline, atropine, or thyroid extract will usually be obvious, and further elaboration is unnecessary.

**3. Palpitation Due to Functional Disorders of Circulatory System.** "Functional" is used here in the ambiguous sense with which it is frequently employed in medicine; namely, that no visible *structural* basis for a disorder is known to exist. "Functional," in this sense, can mean that while no structural lesions, gross or microscopic, have been discovered, a measurable disturbance of function can nevertheless be demonstrated. "Functional" is a term also applied to symptoms or syndromes in which neither structural nor measurable derangements of function are operative. Both types of functional disorder of the circulatory system are recognized, and in each palpitation is a prominent symptom.

**IRRITABLE HEART** ("EFFORT SYNDROME," "NEUROCIRCULATORY ASTHENIA"). These various terms are unsatisfactory but are employed because they are widely used. The characteristic symptoms of this syndrome are those that may appear in any normal individual who has performed a strenuous physical effort: palpitation, dyspnea, dizziness, weakness, faintness, occasional syncope, tremor. The essential difference between patients with an "irritable heart" and normal persons resides in the fact that the symptoms characteristic of strenuous effort appear in the former group on performance of a relatively mild exertion. Recent observations have thrown considerable light on what has hitherto been an obscure problem; namely, the mechanisms whereby symptoms are induced in patients with the effort syndrome. These investigations have demonstrated that in a high percentage of such individuals definite abnormalities of the circulation exist. The cardiac output may be increased or decreased beyond the normal range, in both instances expressions of the faulty reflex mechanisms that automatically adjust the circulation to the needs of the body. In other words, some of the patients with

irritable hearts do not suffer from a simple neurosis, as has been the commonly accepted opinion, but actually have as the basis of their symptoms a measurable alteration of circulatory function, in many individuals based on anxiety and emotional stress, but in other patients resulting from various diseases.

The symptoms encountered in those patients in whom the disorder is primarily psychogenic are very much the same as those observed in a wide variety of other disorders: the convalescent period following an acute febrile illness, chronic febrile states, thyrotoxicosis, anemia, postural hypotension, and others. In all these the same faulty reflex mechanisms are operative. It is probable that the same explanation holds for the palpitation seen in the menopausal syndrome, aside from the enhanced nervous tension often seen in this condition.

**CARDIAC NEUROSIS.** Palpitation is a common and sometimes leading symptom in patients who demonstrate no structural or functional abnormality by any known method of examination, and to this group the term "cardiac neurosis" is frequently applied. (The term is unfortunate in that it tends to stress the cardiac rather than the emotional component. The disorder might more properly be called "anxiety state with cardiac symptoms.") These patients are recognized by the usual findings that are associated with the neurotic personality, and at the present time it must be assumed that the palpitation of which they so frequently complain is due either to the overactive action of the heart known to be present in anxiety states, or, if the complaint is made when examination reveals an apparently normally beating heart, to the fact that the individual has so low a threshold for the appreciation of sensory stimuli that he is aware of such ordinary activity of the heart as would be imperceptible to the normal person.

The palpitation that is felt by many individuals when lying on the left side—even by those who are not unduly sensitive—is clearly due to the better transmission of the heart sounds to the ear. Lifting the head from the pillow will bring out a striking diminution or immediate disappearance of the symptom.

**4. Onset of Congestive Failure.** Usually this state is not attended by palpitation except when auricular fibrillation is the precipitating cause.

In exceptional cases, however, and especially in hypertensive subjects, this symptom, previously present in mild degree, becomes aggravated shortly before the onset of cardiac failure, and then disappears as myocardial insufficiency becomes marked. This is a rare and relatively unimportant cause of palpitation.

The most common causes for palpitation have been enumerated and briefly discussed. Since this symptom occurs in such a wide variety of disorders which have no common or closely related underlying disturbance of structure or function, aside from the alterations of heart rate and output per beat, it is impossible to follow closely any predetermined plan of study in elucidating the significance of the symptom. The exact procedure will vary, of course, with the circumstances under which the patient is seen. The following table summarizes the main points of information that will be ascertained in the history:

*Does the palpitation      If so, suspect:  
occur:*

as isolated "jumps" or "skips"?	extrasystoles
in attacks, known to be of abrupt beginning, with a heart rate of 120 or over, of regular or irregular rhythm?	paroxysmal rapid heart action
independent of exercise or excitement adequate to account for the symptom?	auricular fibrillation, auricular flutter, thyrotoxicosis, anemia, febrile states, hypoglycemia, neurocirculatory asthenia, cardiac neurosis
in attacks developing rapidly though not absolutely abruptly, unrelated to exertion or excitement?	hemorrhage, hypoglycemia, tumor of the adrenal medulla
in conjunction with the taking of drugs?	tobacco, coffee, tea, alcohol, epinephrine, ephedrine, aminophylline, atropine, thyroid extract
on standing?	postural hypotension
in middle-aged women, in conjunction with flushes and sweats?	menopausal syndrome
when the rate is known to be normal and the rhythm regular?	cardiac neurosis

These questions, and others formulated according to the circumstances of the individual case, will serve to suggest the additional lines of inquiry that may be necessary for analysis and appraisal of the palpitation.

Two points merit special emphasis. The first is that in a person with a regular rhythm the presence of palpitation is usually good evidence against the simultaneous presence of myocardial failure. The second point is that as a rule palpitation produces anxiety and fear out of all proportion to its seriousness. Thus a vicious cycle may be created, the emotional disturbance induced by the symptom tending to aggravate it. When the cause has been accurately determined and its significance—or, more commonly, its insignificance—explained to the patient, the

symptom is often ameliorated and may disappear entirely.

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## 12

### Anoxia, Cyanosis, and Polycythemia

M. F. Mason, M. M. Wintrobe, and T. R. Harrison

#### Mechanisms of Anoxia

#### Effects of Anoxia

#### Cyanosis

#### Polycythemia in Relation to Cyanosis

"Anoxia" actually means absence of oxygen, a state which is incompatible with life, but it has been widely used to indicate an inadequate supply of oxygen rather than a total absence. A more accurate term would be "hypoxia," but because of the sanction of time to the usage of anoxia it will be retained in the discussion to follow. It is important to distinguish between anoxia and asphyxia, the latter term indicating a state characterized by carbon dioxide accumulation as well as by oxygen deficit. In the physiologic sense anoxia refers to oxygen deficiency in the tissues of the body.

Recent investigations have shown that the sole action of oxygen in the body is that of accepting electrons and combining with hydrogen ions to form water. (Molecular oxygen, having no

electric charge, becomes electronegative by absorbing electrons, and thereby becomes capable of uniting with the positively charged hydrogen ions.) The oxygen receives electrons largely from cytochrome oxidase, which in turn is supplied with electrons from preceding steps in the oxidative system. Since the entire process will be considered in some detail in Chapter 30, detailed discussion of the oxidative mechanisms may be deferred. It should be emphasized, however, that energy production within the body is dependent on the breakdown of foodstuffs, and that such breakdown is ultimately dependent on an adequate rate of removal of the electrons and hydrogen ions so produced—i.e., on the union of hydrogen and oxygen to form water. Whenever the concentration of oxygen (see below) declines, it appears that the concentration of certain metabolites (of which lactic acid is an example) increases, and such increase apparently has the twofold effect of producing

some of the clinical manifestations of anoxia, and at the same time of tending to maintain the actual rate of over-all oxygen consumption at a normal level, or nearly so, despite the reduction in oxygen concentration.

Since oxygen is a gas at ordinary temperatures and pressures, it is usual to speak of "tension" or "pressure" rather than "concentration." The terms "tension" and "pressure," which are readily understandable when applied to a free gas, sometimes lead to confusion when applied to a gas in solution. Such confusion may be avoided by recalling certain general principles.

1. The partial pressure of a free gas, under standard conditions of temperature ( $0^{\circ}$  C.) and pressure (760 mm. Hg), depends on its percentage by volume. Thus at sea level, in dry air which consists of about 21 per cent oxygen, the partial pressure of this gas is approximately 160 mm. Hg. In the case of alveolar air which is saturated with water vapor, the partial pressures of oxygen and carbon dioxide are approximately 105 and 40 mm. Hg, respectively.

2. The tension (or pressure) of a gas in a liquid is expressed in terms of the gas pressure necessary to dissolve the actual amount of the particular gas present in the particular liquid at a given temperature. The actual concentration of free or uncombined gas in a liquid is, therefore, related to inherent solubility of the given gas in the given liquid, to the partial pressure of the gas to which the liquid is exposed, and to the temperature.

3. In the case of *arterial blood plasma*, which is ordinarily exposed to an alveolar oxygen tension of about 100 to 110 mm., the normal oxygen tension is 100 to 110 mm., but the solubility of oxygen being low, the actual concentration of dissolved oxygen is about 0.4 ml. per 100 ml. Such a value may appear unimportant, but since it represents the oxygen tension, which is the chief determinant of the quantity of oxygen which hemoglobin releases or takes up, it is a matter of first moment.

4. Oxygen deficiency or anoxia is ordinarily not related to an actual decline in the amount of over-all oxygen consumed relative to the need, for such a decline occurs only with the most profound degrees of anoxia. As a rule, the anoxic subject suffers not from decline in oxygen consumption, but rather from the consequences of a

decline in the oxygen tension at the locus of its chemical action.

### MECHANISMS OF ANOXIA

The classification of the types of anoxia usually employed is that of Barcroft, as modified by Van Slyke, who subdivided anoxic states into four main divisions, in terms of the mechanisms involved:

- I. *Anoxic anoxia*; i.e., anoxia consequent to failure of the arterial blood to become normally saturated with oxygen.
- II. *Anemic anoxia*; i.e., anoxia due to a decline in the quantity of hemoglobin capable of transporting oxygen per unit volume of blood.
- III. *Stagnant anoxia*; i.e., anoxia which is the result of stagnation of blood in the tissue capillaries.
- IV. *Histotoxic anoxia*; i.e., failure of utilization of oxygen which otherwise adequately reaches the tissues.

Expansion in knowledge of the physiology of the circulation occurring since this classification was proposed has made some modification of it desirable, and for the purposes of the discussion to follow, a somewhat different classification will be employed, viz.:

- I. *Arterial anoxia*; i.e., anoxia consequent to failure of the arterial blood to become normally saturated with oxygen:
  - A. Diminished oxygenation in lungs
  - B. Admixture of venous blood via shunts
- II. *Anemic anoxia*; i.e., anoxia due to a decline in the quantity of hemoglobin capable of transporting oxygen per unit volume of blood:
  - A. Diminished concentration of hemoglobin
  - B. Chemical alteration of hemoglobin
- III. *Circulatory anoxia*, arising from:
  - A. Ischemia
  - B. Stagnation
- IV. *Metabolic anoxia*, arising from:
  - A. Need for oxygen beyond the capacity of normal respiratory and circulatory mechanisms to supply it
  - B. Failure of tissues to employ available oxygen

These may now be considered in more detail.

**Arterial Anoxia.** This term refers to a condition in which the oxygen tension is diminished in the arterial blood, with consequent diminution in the percentage saturation of the hemoglobin (fig. 20). Such a diminution in the arterial

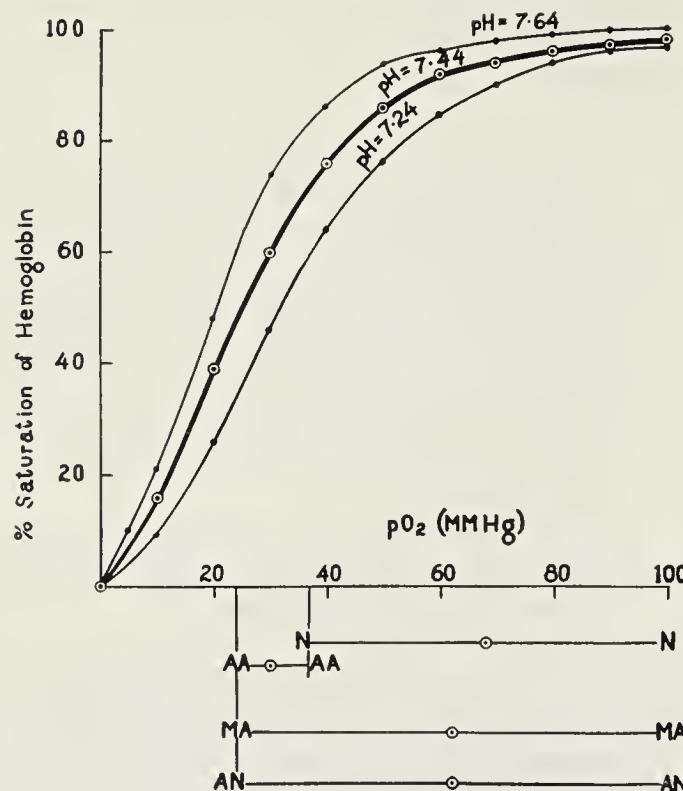


FIG. 20. Relationship between oxygen tension and oxygen saturation of the hemoglobin of the blood. The heavy line is for blood at pH 7.44. The curves to the right and left are those for bloods at pH 7.24 and 7.64, respectively, indicating quantitatively the magnitude of the Bohr effect for hydrogen-ion concentration changes of these magnitudes.

Thus, at about the middle of the curve shown for pH 7.44, a fall in pH to 7.24 will decrease the saturation of hemoglobin by about 15 per cent, without change in oxygen tension. Hence, during severe muscular exercise the increase in tissue acidity makes oxygen more available to the muscles. At high altitudes, or under conditions which lower alveolar carbon dioxide tension, the shift in the dissociation curve upward and to the left makes it possible for the blood to take up more oxygen at a given oxygen tension. It should be realized that the Bohr effect, although of especial importance under certain conditions of adverse environment or physiologic stress, plays a significant role in oxygen exchange, even under normal resting conditions.

Beneath the abscissas are plotted the calculated arteriovenous oxygen tension differences, upon the presumption of the right-heart venous oxygen content normally being 5 vol. % less than the arterial content, and with constant cardiac output in the following states: N = normal subject, arterial oxygen content 20 vol. %; AA = same subject suffering from arterial anoxia sufficient to lower the arterial oxygen content to 14.6 vol. % (= 73 per cent saturation), but with oxygen consumption unaltered; MA = same subject with 100 per cent increase in oxygen consumption; AN = anemic

oxygen tension may be brought about when there is a corresponding decline in the tension of oxygen in the inspired air, the respiratory mechanism remaining otherwise unimpaired, and when there is interference with the free passage of air through the respiratory pathways, or when there is disease of the lungs. In the case of many types of chronic pulmonary disease attended by fibrosis and obliteration of the capillary vascular bed, arterial anoxia does not occur because there is no significant volume of circulation through the unaerated portions. The occurrence of arterial anoxia is favored by those disorders, such as pulmonary edema and emphysema, in which there is considerable circulation through areas of the lungs which have impaired ventilation.

Another, but less common, cause of arterial anoxia is a congenital malformation of the heart of such a type as to allow unaerated blood to pass into the arterial system. Congenital heart disease of several types is attended by abnormal communications between the right and left sides of the heart. Under ordinary conditions the transfer of blood tends to be from the left side, with its higher pressure to the right side. However, under certain conditions, such as exist in patients with the combination of pulmonary stenosis and an interventricular septal defect, or in patients with a three-chambered heart, a

subject, arterial oxygen content 10 vol. %, with arterial saturation and oxygen consumption same as in normal subject. The heavy dots indicate the mean oxygen tension in each instance.

It should be understood that the conditions depicted in these states are exaggerated in comparison to those actually obtaining in such subjects. Thus, the consequences of the normal Bohr effect and of temperature upon the dissociation curve are ignored. In instances of arterial anoxia, increases in circulating hemoglobin usually occur, and the venous tension is still further modified by the Bohr effect in a direction depending upon the mechanism by which the arterial unsaturation is produced. In the case of metabolic anoxia, the effects of temperature increase and rising cardiac output lessen the degree of anoxia which otherwise would obtain. In the case of anemic anoxia, a rising cardiac output tends to lessen the anoxia.

In spite of these simplifications, the diagram indicates the principles concerned in the understanding of the relative severity of anoxias produced by different mechanisms. The quantitative tensions involved vary for each tissue, depending upon a number of factors, but chiefly upon the normal volume of blood flow per unit time per unit mass of tissue, and the inherent oxygen consumption of the tissue concerned. The actual tissue tensions, in any event, are less than the corresponding capillary tensions.

significant proportion of the blood returning to the right side of the heart passes directly into the left side without moving through the lungs. It is under such conditions that arterial anoxia tends to occur (Chapter 236).

When anoxia occurs as the result of decline in oxygen tension in the inspired air, the respiration is stimulated, the alveolar ventilation increases, and the carbon dioxide tension in the alveoli and in the arterial blood declines. This causes a shift in the oxygen dissociation curve to the left (fig. 20), and enables a given tension of alveolar oxygen to cause a greater degree of oxygen uptake by the hemoglobin (the Bohr effect).

When, on the other hand, anoxia results from interference with the passage of air into the lungs, or from impairment of oxygen diffusion in the lungs, the resulting respiratory stimulation is less effective in causing carbon dioxide elimination. The carbon dioxide tension, therefore, remains normal, or rises; and the oxygen dissociation curve tends to remain unchanged, or to move to the right (fig. 20). Under such conditions the percentage saturation of the hemoglobin in the arterial blood at a given level of alveolar oxygen tension does not rise, and may even decline. Thus arterial anoxia and cyanosis are likely to be more marked in proportion to the degree of depression of alveolar oxygen tension when such depression results from pulmonary disease, than when the depression results from a decline in the partial pressure of oxygen in the inspired air.

Inspection of figure 20 illustrates why the respiratory mechanisms may be considerably impaired, without a significant degree of arterial anoxia developing. This is because the properties of hemoglobin are such that its dissociation curve is practically flat above 100 mm. of oxygen tension, and almost so down to about 80 mm. When the tension of oxygen in the alveoli falls below this point, at which the slope of the dissociation curve tends to become more nearly vertical, a rapid decline in the amount of oxygen in the arterial blood occurs. A clear understanding of the physiologic significance of this S shape of the oxygen dissociation curve enables one to understand why anoxia and cyanosis do

not occur in significant degree in a person ascending in an airplane to about 8000 feet above sea level, and also why the change from 8000 to 16,000 feet is associated with development of well-marked cyanosis and anoxia. At 8000 feet the tension of oxygen in the inspired air is about 120 mm. Hg, and the alveolar tension approximately 80 mm. Hg. At such pressures of oxygen the blood is well-nigh completely saturated. On the other hand, at 16,000 feet the oxygen tensions in atmospheric air and alveolar air are about 85 and 50 mm. Hg, respectively, and inspection of the oxygen dissociation curve shows that under such conditions the arterial blood is only about 75 per cent saturated. This leaves an excess of 25 per cent of the hemoglobin in the reduced form, and it is the amount of this reduced hemoglobin, as described later, which determines the degree of cyanosis.

The hyperventilation associated with arterial anoxia causes a shift in the oxygen dissociation curve. The hemoglobin will, under these circumstances, take up oxygen more readily at a given oxygen tension (Bohr effect).

If the blood enters the arterial end of the capillary already inadequately saturated with oxygen, and if the flow of blood through the tissues and the oxygen consumption of the tissues remain constant, then the amount of oxygen extracted in the tissues as the blood passes through the capillaries will remain constant. Therefore, the venous blood emerging from the capillary will be further reduced in oxygen by an amount corresponding to the initial abnormal reduction in the arterial blood. If we remember that oxygen is leaving the blood throughout the passage through the capillary, and think in terms of the mean capillary oxygen tension, then it is clear that in the case of arterial anoxia this value is lowered throughout the entire length of the capillary. It also follows that the mean or average capillary oxygen tension must be considerably reduced as the result of any significant degree of arterial anoxia which reduces the oxygen pressure at the arterial as well as the venous end of the capillary (fig. 20).

The clinical features of arterial anoxia depend upon the acuteness with which it sets in. Barcroft has pointed out that when anoxia develops rapidly the picture resembles drunkenness, while when it develops slowly the condition simulates fatigue. In either case cyanosis is likely to be

striking, and when the arterial anoxia is of long duration, clubbing of the fingers usually appears.

**Anemic Anoxia.** This term is somewhat confusing because it includes different states, one of which is associated with anemia, and others of which may be accompanied by a normal amount of hemoglobin or hemoglobin derivatives in the blood. Any deficiency in the concentration of hemoglobin per unit of blood is attended by a corresponding decline in the oxygen-carrying power. Under such conditions the tension of oxygen in the arterial blood remains normal, but the absolute amount of oxygen transported per unit volume of blood is diminished. As the anemic blood passes through the capillaries and the usual amount of oxygen is removed from it, the tension of oxygen in the venous blood declines to a greater degree than would normally be the case. This is illustrated in figure 20. If other conditions, such as the volume flow of blood and the metabolic rate, remain constant, the absolute amount of oxyhemoglobin in the venous blood of an anemic patient is diminished. However, since the total quantity of hemoglobin is decreased, and the absolute amount of reduced hemoglobin is not increased, cyanosis does not tend to occur.

Anemic anoxia may also arise as a result of the conversion of normal hemoglobin to non-oxygen-carrying derivatives such as methemoglobin or sulfhemoglobin. From the standpoint of anoxia, the patient is in the same state as if the abnormal hemoglobin were not present at all. Thus, in so far as the supply of oxygen to the tissues is concerned, the conditions characterized by abnormal types of hemoglobin correspond to anemic anoxia. On the other hand, the clinical picture of this type of anemic anoxia is quite different from the more usual type, in that there is a large amount of unoxygenated hemoglobin in the blood, and hence cyanosis is apt to be striking.

Carbon monoxide intoxication is accompanied by the equivalent of anemic anoxia in that the hemoglobin which is combined with the carbon monoxide is unavailable for oxygen transport. But, in addition to this, the presence of carboxyhemoglobin increases the affinity of normal hemoglobin for oxygen at low oxygen tensions (i.e., shifts the lower portion of the dissociation curve of hemoglobin to the left), so that the oxygen can be unloaded only at lower tensions. It is this latter effect which makes a given degree

of reduction in oxygen-carrying power by formation of carboxyhemoglobin produce a far greater degree of tissue anoxia than the equivalent reduction in hemoglobin due to simple anemia.

The tension of oxygen in the venous blood is decreased in both conditions—anemic anoxia and arterial anoxia. The tension of oxygen in the arterial blood is not reduced in anemic anoxia (see figure 20). Therefore, in anemic anoxia the decrease in mean capillary oxygen tension and in tissue oxygen tension is less than in arterial anoxia. Patients with anemia of moderate severity do not exhibit any of the manifestations of oxygen deficiency while at rest, but are likely to display such symptoms on exertion. When anemia becomes of very severe degree, symptoms of anoxia may be present even at rest.

**Circulatory Anoxia.** Even though the blood is normal as regards quantity and type of hemoglobin and is normally saturated with oxygen, and even though the oxygen consumption of the tissues remains normal, a diminution in the tension of oxygen at the venous end of the capillary will necessarily occur if the volume flow of blood through the tissues is reduced (fig. 20). Such a decrease in circulation to the tissues may be purely local, as in the case of obstruction to arteries and veins, or may be more general, as in the case of circulatory failure (Chapter 14). When the obstruction is local and is primarily on the arterial side of the circulation, the affected members are likely to be pale, often with a slight bluish tint, and cold. When the obstruction affects the veins primarily, the tissues may be swollen and blue. The circulatory type of anoxia may, therefore, be subdivided into two varieties, the ischemic type in which the arterial flow is primarily affected, and the congestive or stagnant type in which the venous flow is primarily at fault.

The term "stagnant anoxia" has been used to designate oxygen deficiency resulting from diminished circulation to a part. However, the term implies that the blood remains in the tissues an abnormally long time, and such is not necessarily the case, for the velocity of blood flow in a part may remain normal, even though the volume flow is reduced. Hence, the term "circulatory anoxia" would seem to be preferable. It should be realized that there are two types of circulatory anoxia, depending on whether the

impairment of circulation is primarily on the arterial or the venous side. In the former case, which might be called "ischemic anoxia," the blood flow through the tissues is reduced, the actual volume of blood in the tissues is less than normal, but the rate of movement of the blood remains relatively normal. In the case of rise in venous pressure the volume of blood in the tissues is increased, the velocity of movement is diminished, and the volume of blood flow per unit of time may or may not be decreased. Because the velocity of flow is diminished under such circumstances, the term "stagnant anoxia" is applicable.

It is apparent that the circulatory type of anoxia differs from the arterial and anemic types in that the two latter types affect all parts of the body, while the circulatory type may be either local or general. When it is local, the clinical symptoms produced depend entirely on the part affected, the symptoms are likely to be absent at rest, and to be apparent in the form of local pain on exertion. The clinical pictures which occur when circulatory anoxia is general, as the result of circulatory failure, are discussed in some detail in Chapter 14.

**Metabolic Anoxia:** (1) INCREASED OXYGEN NEED OF TISSUES. Even though the oxygen diffusion into the arterial blood be unhampered, the hemoglobin be qualitatively and quantitatively normal, and the volume of circulation per unit of time be normal, the tension of oxygen in the venous blood may be reduced if the oxygen consumption of the tissues is elevated, as occurs in fever and in thyrotoxicosis (fig. 20). Under such conditions the circulation may be considered as being deficient relative to the metabolic requirements. Thus this type of metabolic anoxia is comparable to circulatory anoxia in that in both conditions the volume flow of blood is decreased relative to the needs of the tissues, the difference in the one case being that the primary defect is in the volume flow of blood, while in the other the primary defect is an increased oxygen need by the tissues.

Ordinarily, the clinical picture of patients with anoxia due to an elevated basal metabolic rate is quite different from that of other types of anoxia, for the skin is warm and flushed and cyanosis is absent.

ABLE OXYGEN. The administration of cyanide leads to a paradoxical state in which the tissues are unable to utilize oxygen, and the venous blood therefore tends to have a high oxygen tension, in consequence of a deficiency of oxygen utilization in the tissue cells. This is an instance of a type of metabolic disturbance in which the defect is not in oxygen supply to the tissues but in the capacity of the tissues to utilize oxygen. Deficiency of a substrate, such as glucose, of certain enzymes, catalytic carriers, or coenzymes, of which the members of the B complex are the best known, may lead to a somewhat similar condition. Although much progress has been made in recent years in the understanding of the complexities of tissue oxidation, there are still large gaps in our knowledge in this regard. Thus far there has not been a general correlation of clinical syndromes with such chemical abnormalities. The subject of disorders of tissue oxidation will, therefore, not be discussed further, but the point should be emphasized that within the next few years we may reasonably expect to learn much of importance in clinical medicine from applications of fundamental advances in this field.

## EFFECTS OF ANOXIA

The symptoms of local oxygen deficiency depend on the tissue affected, are therefore protean in nature, and will not be discussed here. When anoxia is general, all parts of the body may suffer some impairment of function, but those parts which are most sensitive to the deleterious effects give rise to symptoms which dominate the clinical picture. The *changes in the central nervous system* are especially important, and here the higher centers are most sensitive. Acute anoxia, therefore, produces impairment of judgment, motor incoordination, and a clinical picture which closely resembles that of acute alcoholism. Where anoxia is long-standing, the symptoms consist of fatigue, drowsiness, apathy, inattentiveness, and delayed reaction time simulating manifestations of severe fatigue. As anoxia becomes more severe, the centers of the brain stem become affected and death usually results from respiratory failure, the gasping reflex—being a primitive mechanism—persisting to the last. As compared to the brain, the phylogenetically older spinal

cord and peripheral nerves are quite resistant, and symptoms due to disturbance of these structures usually do not appear.

Some of the *metabolic effects of anoxia* are well known in regard to the liver and muscles. In these structures the breakdown of the primary foodstuff, carbohydrate, normally proceeds anaerobically (i.e., without oxidation) to the formation of pyruvic acid. The further oxidation of pyruvic acid requires the availability of oxygen, and when this is deficient the breakdown is impaired and increasing proportions of this substance become reduced to lactic acid, which cannot be further broken down anaerobically (Chapter 30). Hence any considerable degree of anoxia is accompanied by an increase in the blood lactate, with decrease in bicarbonate, a corresponding acidosis, and a marked change in the character of the metabolic processes in muscle and in liver. The details of the changes in other tissues are less well understood and need not be discussed further.

Anoxia has important *effects on respiration*. In the anesthetized animal, oxygen deficiency produces respiratory stimulation through the carotid body with its chemoreceptor mechanism. Recent studies make it improbable that the conscious man is affected by this mechanism, which is probably important in states of anesthesia and coma. In the normal man it appears that anoxia has a double effect on the respiratory center. It renders this structure less sensitive and at the same time tends to stimulate it, as the result of accumulation of acid (lactic?) in the center. Whether or not respiration will be stimulated or depressed by anoxia, therefore, depends upon the resultant of these several actions. The degree of depression of the respiratory center is apparently related to the degree of anoxia. On the other hand, the degree of acid accumulation in the center tends to reach a maximum, once anoxia becomes sufficiently marked to interfere with oxidation and cause acid accumulation in the cell. For this reason mild to moderate anoxia ordinarily causes a stimulation of breathing, the effects of acid accumulation predominating over those of direct depression. However, profound anoxia is likely to cause the effects of the depression of the center to dominate over those of the stimulation caused by accumulation of acid within it. When a patient becomes comatose or unconscious as

the result of anesthesia, the effects of anoxia may be markedly modified by the chemoreceptive mechanism of the carotid body.

The acute effects of anoxia on *the reaction of the blood* are likewise complicated, because two different antagonistic influences are at work. If the breathing is stimulated by anoxia, the resulting increase in ventilation, with loss of carbon dioxide, tends to make the blood more alkaline. On the other hand, the diffusion of unoxidized lactic acid from the tissues into the blood tends to make the blood more acid. In either case the total bicarbonate, and hence the carbon dioxide-combining power, tends to be diminished. With mild anoxia there is likely to be respiratory alkalosis; severe anoxia is attended by metabolic acidosis (see Chapter 29).

One of the important mechanisms of compensation for prolonged anoxia is an increase in the amount of hemoglobin in the blood. This is apparently the result of a direct effect of anoxia on the bone marrow, because a well-marked reticulocytosis has been demonstrated, in addition to splenic contraction and other mechanisms for increasing the circulating red cell mass. The increase in hemoglobin and in red cell concentration begins within a few hours after the onset of anoxia, and does not reach its peak for several weeks. Values up to 40 per cent above the normal are not unusual for individuals residing at high altitudes.

The *heart*, although relatively sensitive to anoxia as compared to most of the structures of the body, is less sensitive than the nervous system, and, consequently, serious manifestations of cardiac impairment do not commonly occur when there is generalized anoxia, for the manifestations arising in the nervous system dominate the picture. It is known that diminished oxygen tension in the tissues favors increase in local blood flow, with increased venous return, and an elevation of the cardiac output. This increase in cardiac work, which is one of the means of compensation for anoxia, may precipitate congestive failure in patients with preexisting heart disease.

Local anoxia of the heart as the result of disease of the coronary arteries is, on the other hand, a common clinical disorder, being associated with angina pectoris when the anoxia is temporary and relative, and with myocardial

infarction when the anoxia is permanent and absolute (Chapter 3).

Renal function, while sensitive to ischemia, is usually not sufficiently impaired by arterial anoxia to produce clinical manifestations. The gastrointestinal tract seems to be more resistant to anoxia than most of the other vital parts of the body.

One of the most impressive clinical manifestations of certain types of anoxia is alteration in the color of the skin, and this phenomenon will, therefore, be discussed in somewhat more detail.

### CYANOSIS

Although the term "cyanosis" in its strictest sense means blueness, it is ordinarily restricted to a special type of blueness—namely, that which is due to an increased amount of reduced hemoglobin, or derivatives of hemoglobin, in the small blood vessels of the skin and mucous membranes. Hence it is to be distinguished from argyria, a condition in which there is a bluish discoloration of the skin as the result of the deposition of silver salts. In the latter condition there is a metallic tint and the blue color persists despite pressure, while the truly cyanotic skin becomes pale when sufficient pressure is exerted to express the blood from the vessels.

Cyanosis is usually most marked in the lips, the nail beds, the ears, and the malar eminences. In the latter region the line of distinction between true cyanosis and the ruddy color which is commonly seen in robust elderly subjects cannot always be clearly drawn. Furthermore, the "red cyanosis" of primary polycythemia must be distinguished from the true cyanosis discussed here.

The fundamental mechanism of cyanosis was shown, by Lundsgaard and Van Slyke, to consist of an increase in the amount of reduced hemoglobin in the minute vessels of the skin. This may be brought about either by increase in the amount of venous blood in the skin as the result of dilatation of the venules and venous ends of the capillaries, or by a decrease in the oxygen saturation in the capillary blood. In general, cyanosis tends to be roughly proportional to the average amount of unsaturation in the capillaries —i.e., to the mean between the amounts of reduced hemoglobin in the arterial and venous blood, respectively. It is the absolute rather than the relative amount of reduced hemoglobin which

is important in producing cyanosis. Thus in a patient with severe anemia the relative amount of reduced hemoglobin in the venous blood may be very large when considered in relation to the total hemoglobin. However, since the latter is markedly reduced, the absolute amount of reduced hemoglobin may still be small. It is for this reason that patients with severe anemia are incapable of displaying cyanosis. Conversely, the higher the total hemoglobin content the greater is the tendency toward cyanosis, and thus patients with marked polycythemia may be cyanotic in the absence of any other demonstrable abnormality. Likewise, local passive congestion, which causes an increase in the total amount of hemoglobin in the vessels in a given area, may cause cyanosis even though the average percentage unsaturation is not altered.

*X* The formation of abnormal types of hemoglobin as the result of various types of intoxication may lead to cyanosis. Among the important intoxicating substances in this respect are acetanilid, sodium nitrate, or nitrite, and hydrogen sulfide, which may be absorbed from the intestinal canal in predisposed subjects (*enterogenous cyanosis*). These substances lead to the formation of met-hemoglobin or of sulfhemoglobin. Carbon monoxide intoxication usually produces a cherry red color rather than a bluish discoloration, because carboxyhemoglobin has a bright red color. Some of the sulfonamides (notably sulfanilamide and sulfapyridine) produce striking cyanosis, the exact mechanism of which is still subject to debate.

Diminished volume flow of blood through the skin may likewise cause cyanosis which is likely to be of the pale grayish type. Peripheral circulatory failure, certain instances of congestive heart failure, arterial or venous obstruction, and exposure to cold constitute examples of cyanosis due to this mechanism. Slight cyanosis of the hands, without cyanosis elsewhere, may be due to local vasomotor influences, causing a reduction in the blood flow. In such instances the hands are cold. Cyanosis associated with normal warmth of the hands is more likely to be indicative of a systemic rather than a local disorder.

Aside from the fundamental factors which have been mentioned, there are certain modifying factors which influence the degree of cyanosis. These include the thickness of the epidermis, the quan-

tity of cutaneous pigment, the color of the blood plasma, as well as the state of the capillaries of the skin. The accurate clinical detection of the presence and degree of cyanosis is difficult, as proved by oxymetric studies.

The *differential diagnosis of cyanosis* may be considered from the standpoint of the following outline:

#### I. Circulatory Disorders:

##### A. Cardiac disease:

1. Congenital (intense cyanosis, clubbed fingers, polycythemia)
2. Acquired (slight cyanosis, no clubbed fingers, no polycythemia)

##### B. Peripheral circulatory failure or local obstruction (pallid or ashen cyanosis, cold extremities)

#### II. Pulmonary Disorders:

##### A. Acute (pneumonia, edema, infarction (no clubbing and no polycythemia))

##### B. Chronic (emphysema, extensive fibrosis (clubbing and polycythemia often present))

#### III. Hematogenous Disorders:

##### A. Polycythemia: Erythrocytosis of high altitudes (cyanosis, more or less clubbing); erythremia (plum red cyanosis, usually no clubbing)

##### B. Abnormality in hemoglobin (no clubbing, minimal polycythemia):

1. Exogenous (acetanilid and various other aniline derivatives—e.g., sulfanilamide; carbon monoxide, etc.)
2. "Enterogenous cyanosis" (nitrates, sulfides)

From a practical standpoint it is useful to divide cyanosis into the *circulatory*, *pulmonary*, and *hematogenous* groups. The circulatory group includes cardiac and peripheral types. When cyanosis is due to acquired disease of the heart, it is usually slight in degree and is accompanied by evidence of mitral stenosis, congestive failure, or both of these conditions. Cyanosis due to congenital lesions is likely to be intense, and to be associated with enlargement of the heart and clubbing of the fingers. Cyanosis dependent on disorders of the peripheral circulation is either local and accompanied by evidence of arterial or venous obstruction, or general and associated

with the manifestations of peripheral circulatory failure or shock (Chapter 14). Pulmonary cyanosis, whether acute or chronic, is accompanied by the clinical and radiographic evidences of the responsible process, while hematogenous cyanosis is associated with polycythemia, or with abnormal pigments in the blood.

In a given patient with cyanosis the following points are likely to be especially important in arriving at a correct interpretation of the cause:

1. The history, particularly as regards the duration (cyanosis present since birth usually is due to congenital heart disease), and the possible exposure to the various drugs or poisons which may produce abnormal types of hemoglobin.

2. Objective evidence by radiographic or physical examination of disorders of the respiratory or circulatory systems.

3. The presence or absence of clubbing of the fingers. (Slight clubbing without cyanosis is frequent in patients with subacute bacterial endocarditis, and may occasionally occur in healthy subjects.) Slight cyanosis of the lips and cheeks, without clubbing of the fingers, is common in well-compensated patients with mitral stenosis, and probably is due to minimal arterial anoxia resulting from fibrotic changes in the lungs secondary to long-standing congestion. The combination of slight cyanosis and slight clubbing is frequent in patients with many chronic diseases of the lungs. Marked clubbing and marked cyanosis occur together most commonly in patients with certain types of congenital cardiac disease, and are seen occasionally in subjects with advanced pulmonary arteriosclerosis (Ayerza's disease), or pulmonary arteriovenous shunts. Cyanosis due to acquired cardiac disease, to acute disorders of the lungs, or to acute intoxications is not associated with clubbed fingers.

4. Spectroscopic examination of the blood for abnormal types of hemoglobin in instances where there is a story of suitable exposure, or where examination of the circulatory and respiratory systems affords no adequate explanation for the presence of cyanosis.

#### POLYCYTHEMIA IN RELATION TO CYANOSIS

It will be noted that in a number of the conditions in which cyanosis occurs, polycythemia develops. The term polycythemia signifies an increase above the normal in the number of red

corpuscles in the circulating blood. This increase usually is accompanied by a corresponding increase in the quantity of hemoglobin and in the volume of packed red corpuscles, although this is not always the case. The increase may or may not be associated with an increase in the total quantity of red cells in the body. It is important to distinguish between *absolute polycythemia*, which refers to an increase in the total red corpuscle mass, and *relative polycythemia*, which occurs when, through loss of blood plasma, the concentration of the red corpuscles becomes greater than normal in the circulating blood. This may be the consequence of abnormally lowered fluid intake, or marked loss of body fluids as occurs in persistent vomiting, severe diarrhea, copious sweating, or acidosis (Chapters 14, 28). In certain types of peripheral circulatory failure there is a loss of plasma into the extracellular fluids. Such a shift takes place largely in the periphery, with the result that the polycythemia may be more marked in capillary blood than in that from central blood vessels.

Because the term polycythemia is loosely used to refer to all varieties of increase in red corpuscles, the terms erythrocytosis and erythremia are preferred in referring to two forms of absolute polycythemia. *Erythrocytosis* denotes absolute polycythemia which occurs in response to some known stimulus; *erythremia* refers to a disease of unknown etiology, also known as polycythemia vera, or Osler-Vaquez disease. Erythremia will be discussed in a subsequent chapter.

Erythrocytosis develops as a consequence of a variety of factors and represents a physiologic response to conditions of anoxia. Sojourn at high altitudes leads to defective saturation of arterial blood with oxygen and stimulates the production of more red corpuscles. Immediately on ascent to a high altitude, symptoms such as fatigue, dizziness, headache, nausea, vomiting, ringing in the ears, and prostration may appear. In most persons adaptation soon occurs, with the development of polycythemia and other compensatory adjustments. However, a disorder may set in insidiously a few years later, or even as long as 20 years after continued residence at high altitudes, leading to the development of a condition known as chronic mountain sickness, or seroche (Monge's disease).

Emphysema is the most common of the chronic pulmonary conditions which may lead to eryth-

rocytosis. Silicosis, with extensive pulmonary fibrosis, is another. Pulmonary arteriovenous fistula represents still another mechanism whereby pulmonary disease may lead to impaired saturation of arterial blood with oxygen, with the consequent development of erythrocytosis and of a clinical picture resembling closely that of certain types of congenital heart disease. Hypertension of the lesser circulation, with pulmonary arterial and arteriolar sclerosis, is associated with a train of symptoms such as asthma, bronchitis, dyspnea, and cyanosis, as well as erythrocytosis—a syndrome known as Ayerza's syndrome, or "cardiacos negros."

The partial shunting of blood from the pulmonary circuit, such as occurs in congenital heart disease, is the most striking cause of erythrocytosis resulting from abnormality in the circulation. Erythrocyte counts as high as 13 million, which are possible only when the red corpuscles are smaller than normal, have been observed in such cases, with volumes of packed red cells even as high as 86 ml. per 100 ml. of blood. The most common defect producing such polycythemia is the tetralogy of Fallot (pulmonary stenosis, defective intraventricular septum, dextroposition of the aorta, right ventricular hypertrophy). Erythrocytosis does not usually occur in patients with acquired heart disease, but occasionally is seen in subjects with mitral stenosis.

Chronic methemoglobinemia and chronic sulfhemoglobinemia are likely to be accompanied by moderate erythrocytosis.

In addition to these rather well-defined factors leading to the development of erythrocytosis, there are several other less-understood circumstances which are known to be associated with such a change in the blood. Thus the polycythemia seen in the newborn infant has been attributed to an impaired oxygen supply in utero, although there is some doubt as to the correctness of this assumption. In the newborn, the red cell count is often not so greatly elevated as the hemoglobin and volume of packed red cells, because the cells are substantially larger than normal. This macrocytosis is actually less marked at birth than in the fetus at earlier stages, and seems to represent a phase in the development of the blood in the newborn. Again, it is known that the administration of cobalt experimentally will produce erythrocytosis. The means whereby this effect is brought about is not clear. Several cases

have been described in which erythrocytosis was associated with the presence of subtentorial tumors and disappeared after their surgical removal. Again, polycythemia has been observed in Cushing's syndrome. The mechanism whereby erythrocytosis develops under these conditions is quite obscure.

To summarize: *Erythrocytosis* may be produced by:

1. Defective saturation of arterial blood with oxygen resulting from (a) decreased atmospheric pressure, and (b) impaired pulmonary ventilation.

2. Abnormality in circulation, due to (a) shunting (congenital heart disease), and (b) in certain patients with chronic cardiac disease, pos-

sibly through diminished blood supply to the bone marrow.

3. Defect in circulating blood pigment.

4. Miscellaneous obscure mechanisms which may possibly operate by causing altered metabolism in the bone marrow.

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## 13

### Alterations in Blood Pressure

William Dock

#### Hypotension

#### Hypertension

##### Classification of Hypertension

##### Hypertensive Retinopathy

##### Hypertension Without Initial Renal Lesion or Dysfunction

##### Renal Hypertension

##### Study of Hypertensive Patients and Management of Hypertension

The arterial blood pressure is determined by peripheral resistance and cardiac output. Exact, direct measurement of arterial pressure is effected by arterial puncture and the use of appropriate manometric devices. In the clinical estimation of arterial pressure, using a pneumatic cuff, palpation and auscultation of the artery, it is essential to have a cuff of appropriate width in relation to the subcutaneous fat pad of the limb. Thus, in the case of the obese patient, it is necessary to use for the arm the type of cuff commonly employed for the leg. It is wise to check the auscultatory systolic level by palpation. As the cuff pressure falls, auscultation should continue until the pressure is almost at zero, to avoid being misled by an auscultatory silent gap between the systolic and true diastolic levels. (Further technical de-

tails concerning the measurement of arterial pressure are offered in an appendix at the end of the chapter on Arteriosclerosis.)

The range of blood pressure compatible with normal activity, when compared with the range of other functions, such as temperature, is wide, and undue stress should not be placed upon variations in blood pressure per se.

The blood pressure in the systemic circuit varies in individuals capable of a hard day's work, between systolic levels of 85 to 300, and diastolic levels of 40 to 160 mm. Hg. In the pulmonic circuit the relative range is much greater: 12 to 120 mm. Hg, systolic; 4 to 30 mm. Hg, diastolic.

In infancy, arterial pressure is below 70/45; it rises in late infancy and early childhood to 80/55, and by adolescence reaches levels of 95 to 110 systolic, and 65 to 80 diastolic. In about one third of the white population of Europe and North America this level is maintained until old age. This state, often erroneously designated as "low blood pressure," is in fact likely to be cor-

related with longevity. In more than a third of the population arterial hypertension, with levels of 150/90, or above, is noted as a transient phenomenon even in early adult life, and as the usual level beyond the age of 60. Even occasional rises in resting levels of pulse and blood pressures are found to be associated with a shortening of the average life span. Hypertension occurs earlier and in a higher percentage of Negroes, both in the United States and in tropical Panama, than in white or Indian populations.

The pressures cited above are the casual levels—those found after brief rest periods in people who are up and about. The basal pressures, determined before morning activity begins on awakening, are lower—90/60 in many healthy whites, and 80 or less in many natives of the tropics and of Asia. Sitting or standing normally raises the diastolic levels 5 to 10 mm. Hg, while exercise, anoxia, or anemia lowers the diastolic and raises the systolic levels.

In those predisposed to hypertension, a rise in systolic and diastolic pressure may be caused by chilling, anger, frustration, anxiety, or even pleasant anticipation of exciting events; others may show no rise, even under the most intense emotional stimuli.

### HYPOTENSION

Hypotension is seen in animal experiments only when there is severe shock, or when death from toxemia is near. It is due to loss of vaso-motor function in the arterioles rather than to loss of central vasomotor control. Destruction of the entire brain stem and cord causes profound hypotension, with unusually powerful response to vasoconstrictor drugs and hormones. It is not necessary to point out that chronic hypotension in man is not usually due to either of these mechanisms.

It has long been customary to speak of adults with levels of systemic arterial pressure normal in childhood, or in natives of the tropics, as having *hypotension*. This is not justified if they feel well and have had such levels all their lives. In many wasting diseases and in adrenal cortical deficiency, the arterial pressure usually falls below the level which the individual has shown in health; hence pressures of 120 down to 80 may be abnormally low for a patient whose normal range is known to have been 20 to 40 mm. Hg higher. Hypotension, then, is the presence of a systolic

level under 80 mm. Hg, or one 20 mm. or more below the subject's usual level when in good health. These, of course, refer to levels measured in the recumbent posture, and after resting long enough for the pulse to drop to a level of 80 per minute or less, or after resting for 15 minutes, if the pulse remains more rapid.

In most subjects the diastolic pressures rise when they sit or stand. In some patients there is a fall, and in a few this fall is so great as to cause weakness, palpitation, or even loss of consciousness. Such patients are said to have postural hypotension, often associated with postural tachycardia. This rarely is seen before the age of 30. The normal rise in diastolic pressure, due to the erect posture, involves the pressure-sensitive nerves in the aortic-carotid zone (vasoreceptors) and the vasoconstrictor nerves in the body, but especially in the splanchnic area. Certain diseases of the spinal cord such as tabes and diabetic neuropathy, as well as sympathectomy, lead to abolition of this reflex and to postural hypotension. Pooling of blood in the veins of the legs, particularly when patients have marked varicosities, or when blood volume is low, as after prolonged bed rest or malnutrition, may cause postural hypotension, even though the nervous mechanism is intact. The degree of postural hypotension produced represents a sensitive index of the activity of sympatholytic drugs.

### HYPERTENSION

Hypertension and arterial disease often occur independently, but the relations between the two disorders are of such importance, and have been interpreted in such widely divergent ways, that it seems desirable to consider them together. They are "so involved and interwoven . . . and in so many cunning resemblances hardly to be discerned, that those confused seeds which were imposed on Psyche as an incessant labor to cull out and sort asunder were not more intermixed."

Hypertension is the symptomatic manifestation of an abnormal state of the circulation, just as fever is a symptom of altered temperature regulation. As a clinical disorder, hypertension may be diagnosed when, on repeated examinations, the pressure is found to be above that normal for adolescents. In North American adults 140/85 may be regarded as abnormally high arterial pressure; for coolies in Peiping 125/80 might have similar significance. Signs and symp-

toms which have been regarded as of hypertensive origin are unusual in white people at levels under 180/100; in China, where the arterial pressure tends to be lower, these may be manifest at pressures no higher than 140/85. In acute hypertension occurring in glomerulonephritis and in toxemia of pregnancy, congestive heart failure, headache, choked disks, and convulsive seizures are the classic manifestations; in the chronic disease, headache, cerebrovascular accidents, dizziness, visual defects, heart failure, and the uremic syndrome may be present. Marked hypertension may persist for decades with normal vision and renal function, normal cardiac silhouettes by x-ray, and normal capacity for work and play.

**Relation of Hypertension to Mechanisms by Which Pressure Is Normally Maintained.** The early students of hypertension sought a single organic or humoral abnormality to explain the disorder. It is now evident that many factors participate in the maintenance of the normal level, and that the whole complex may be deranged in some instances, two or more factors in most cases.

Because the vascular tone is the most important factor, changes in cardiac output or in blood volume are of relatively little importance in experimental or clinical hypertension. When a hypertensive patient is bled or has a hemorrhage, the arterial pressure is usually well sustained, even though blood volume and cardiac output are below normal levels. While hypertension is not rare in elderly patients with polycythemia and high blood volumes (Gaisböck's syndrome), many patients with high blood volumes—such as cyanotic congenital cardiaes—usually have normal arterial pressures, and those with the highest pressures usually have normal blood volumes and cardiac outputs. If they develop heart failure, hypertensive persons usually have a rise in blood volume but a fall in cardiac output.

In the experimental hypertension which follows section of the depressor nerves and carotid afferent nerves, cardiac output is high and peripheral resistance only moderately increased. The rarity of these characteristic changes in human cases of hypertension makes it unlikely that loss of depressor tone is an important feature of any of the clinical disorders.

Peripheral resistance is calculated by dividing arterial pressure by cardiac output, and is regularly increased in the clinical disorder and in that

evoked in animals by manipulation of the kidneys or renal arteries. Pressure measurements at various points from the heart to the capillaries show that most of the resistance, normally and in hypertension, is in the arteriolar segment. Relatively small changes in caliber cause marked changes in resistance, which varies inversely as the fourth power of the radius of the lumen. Thus a decrease of 10 per cent in the average arteriolar lumen will lead to a rise of 35 per cent in mean arteriolar resistance and in blood pressure. Such decreases in lumens may be due either to (1) a decrease in vasodilator tone, (2) a rise in sympathetic tone, (3) a humoral agent which raises smooth-muscle tone in arterioles, or (4) a humoral agent which potentiates either neural or humoral tonic effects.

So little is known of vasodilator mechanisms that (1) cannot be evaluated in experimental or clinical hypertension. One theory of renal hypertension is that a normal vasodilator, or inhibitor of vasoconstrictor tone, is constantly being formed by the kidney, and that this ceases when the kidney is manipulated or removed.

The participation of epinephrine or of substances produced by the kidney, and acting, as epinephrine does, on arterial walls, has long been under study in relation to hypertension. No such substance has been demonstrated in chronic hypertension, although angiotonin, a smooth-muscle stimulant formed by action of a renal protein on serum globulin, has been detected in renal vein blood in acute hypertension. Substances which act like ephedrine to potentiate epinephrine also have been detected in renal hypertension. ~~Epinephrine causes vasodilatation in the heart muscle and in voluntary muscles~~, and a fall in skin temperature due to local intensity of its action. It increases cardiac output. Since the cardiac output and skin temperature remain normal in both experimental renal, and various types of clinical hypertension, it is unlikely that epinephrine or epinephrine potentiators play a part in these conditions.

In chronic renal hypertension, and in most clinical cases, agents which block or reduce sympathetic tone cause at least a transient fall of pressure to or below the normal levels. Cord section, sympathetic denervation, and tetraethylammonium salts, as well as dioxane and ergot derivatives, have all been shown to alter hypertensive levels. Vagal section, chilling, ether

anesthesia, and emotional factors which raise normal sympathetic vasomotor tone are effective in further elevating the pressure in hypertensive individuals of various types. It is therefore inescapable that one important factor, if not the most important factor, in all cases of hypertension is a high level of vasomotor tone.

When pressor drugs such as tyramine or epinephrine are injected into normal animals, the sympathetic tone is largely abolished, due to reflexes from the carotid sinus and other depressor sensory areas. Since vasomotor tone is high and easily augmented in hypertension, it seems certain that none of these substances is present in abnormal amounts, except in the hypertension associated with chromaffin tumors. In these, pressure rises when histamine is given intravenously, and falls when adrenolytic dioxane compounds are administered. Normal subjects usually display a fall, and no change, respectively, under the same circumstances. These phenomena are not observed in hypertension due to any other cause, and it seems safe to conclude that in them epinephrine plays no greater role than in normal persons. Since normal or even elevated pressure levels occur in patients whose adrenal glands have been completely destroyed by tuberculosis, when the sodium metabolism is regulated by substitution therapy, the role of epinephrine in blood pressure regulation seems negligible. Its emergency value, in diverting blood from skin, kidneys, and viscera to heart, brain, and voluntary muscles, is undoubted.

Normal pressure levels, and those found in most types of hypertension, seem to be regulated by the vasomotor center and sympathetic nerves. The vasomotor center, located in the brain stem at the level of the medulla and pons, is apparently altered in its "set" in most cases of hypertension, but blood flow to the tissues is normal and responds normally to stress.

### CLASSIFICATION OF HYPERTENSION

Patients with recurrent episodes or continuous level of hypertension fall into three main etiologic groups: (1) renal—congenital or acquired renal lesions presumably antedate and evoke the change in blood pressure; (2) endocrine—adrenal cortical or medullary dysfunction, due to tumor or hyperplasia, is accepted as the main causative factor; (3) unknown etiology—psychogenic and

endocrine factors often appear to influence the levels of blood pressure in these cases.

From the standpoint of prognosis, hypertension may be divided into the benign and malignant types. The former term should indicate all types of hypertension which pursue a slowly progressive course regardless of cause, but is usually reserved for those instances in which the underlying cause is obscure. The term "malignant hypertension" is used for patients with diastolic levels over 120 mm. Hg, marked vascular retinopathy, and early renal or cardiac insufficiency. It is commonly superimposed on the benign type, but the process may progress so rapidly as to be considered malignant from the outset. The relationship of these processes to each other is considered in more detail in Chapter 243.

The term "essential hypertension" is used by some to indicate all hypertension except that due to preexisting renal disease; others use the term to refer to hypertension of unknown origin; still others use it to refer to the benign as contrasted with the malignant type. In view of this confusion, the term "essential hypertension" will not be employed in the discussion to follow.

### HYPERTENSIVE RETINOPATHY

Careful inspection of the retina affords information of the greatest value in persons with hypertension. The earlier changes are confined to the vessels, and comprise "nicking" of the veins by the arteries and some variations in caliber of the arteries (figs. 21, 22, 23). As the process becomes more severe, small, flame-shaped, red patches (hemorrhage) and punctate white spots (exudate) appear. At a later stage the areas of hemorrhage and exudate may be confluent and may conceal the normal architecture of the retina. When hypertension is especially rapid in its development, the typical signs of papilledema (obliteration of the cup of the disk, loss of clear disk margin, embedding of the vessels in the disk) may be observed.

Because papilledema usually reflects changes in the brain and the spinal fluid pressure, and exudate and hemorrhages parallel the progress of renal arteriolar lesions, the state of the retinas is of primary importance in evaluating the severity of hypertensive disease. The level of the blood pressure is much less important.

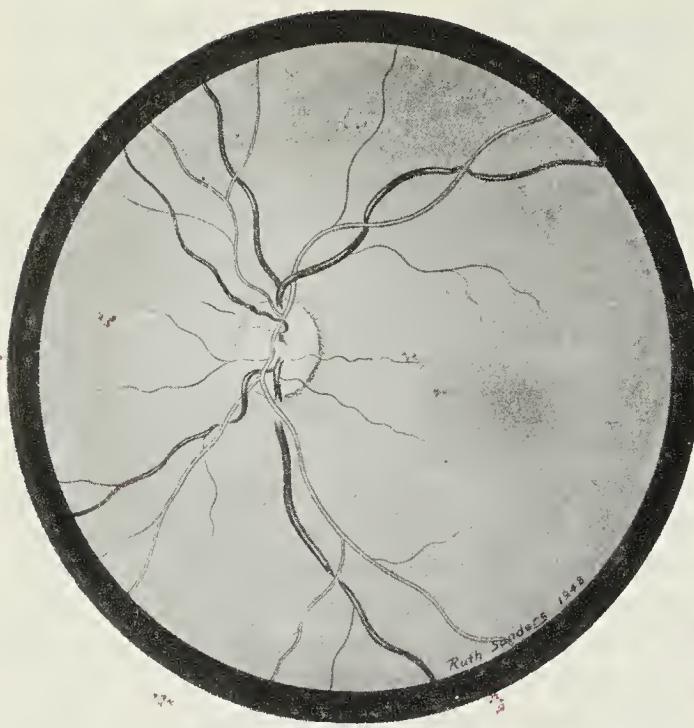


FIG. 21. Nicking of the veins by the arteries is illustrated as the earliest change of vascular retinopathy. (This figure republished by permission of Dr. Samuel A. Shelburne and the editor of *Archives of Internal Medicine*.)

#### HYPERTENSION WITHOUT INITIAL RENAL LESION OR DYSFUNCTION

The commonest type of hypertension is that which first manifests itself as emotional instability of pulse and arterial pressure in the late teens and early twenties. The course is now well



FIG. 22. The changes here are somewhat more advanced, in that there is a definite gap between the arteries and the veins. Some localized alterations in the caliber of the arteries will be noted. (This figure republished by permission of Dr. Samuel A. Shelburne and the editor of *Archives of Internal Medicine*.)

known from follow-up on college, insurance, and military physical examination records. Periods of elevated pressure become more numerous and prolonged, basal (morning) levels gradually rise, remissions of months or years may occur, but between the ages of 45 and 55 most of these individuals have developed true hypertension. However, many who have, on examination, systolic pressures under 140 in the twenties or thirties may also develop true hypertension before 45 years of age, and new cases continue well up into the sixties or later.

At the onset, and in some cases for years or decades, the altered blood pressure is the only

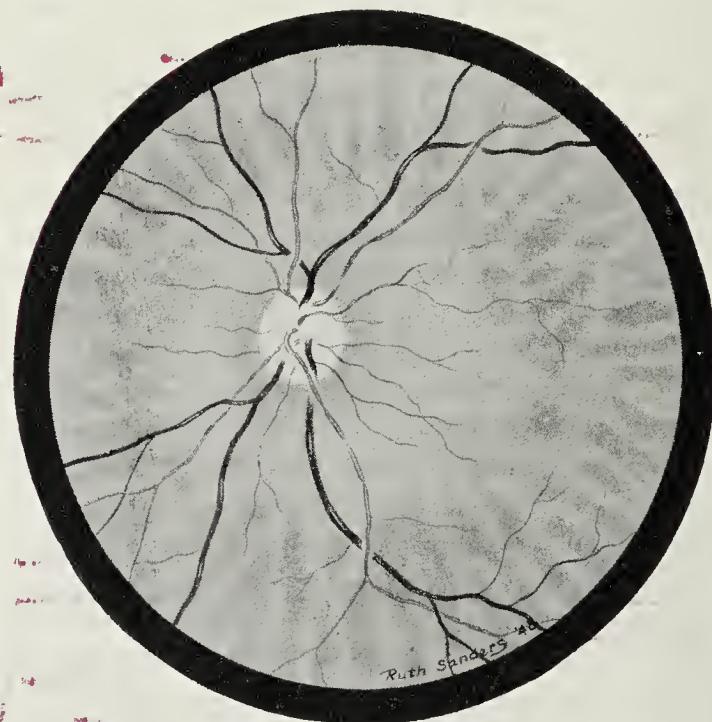


FIG. 23. The alterations are somewhat more advanced. Arteriovenous nicking is striking. Variations in the arterial caliber are more marked than in figure 22. (This figure republished by permission of Dr. Samuel A. Shelburne and the editor of *Archives of Internal Medicine*.)

demonstrable abnormality. However, recent work has shown that renal vasoconstriction and reduced renal blood flow are usually present, that wastage of sodium during the first day of rigid salt-free diet is less than in normal persons, and that desoxycorticosterone evokes a prompt pressor response in these people, but not in normal individuals. The renal vasoconstriction apparently is neurogenic, and can be released by pyrogens given intravenously. While this benign hypertensive state is more complex than a simple rise in vasomotor tone, it is not preceded by organic lesions of the vessels of the kidney, and its course is like that of many nervous involutions, such as that causing intention tremor. This

latter first appears after stress in early adult life, is accentuated by increased fatigue or anger, and becomes constant by the age of 50 in many people. It involves the muscles of the hands, arms, and face; rarely those of the legs. Benign hypertension may represent a similar loss of control of the vascular part of the muscular system, due to involution in the brain stem. It shows, as does tremor and baldness, a familial incidence and pattern of progress. It is increased, as is tremor, by psychogenic disturbances of all sorts.

**Adrenal Medulla.** *Pheochromocytoma*, usually in the adrenal, may cause paroxysmal, and later sustained but variable, hypertension. This may occur at any age, may not be associated with noticeable signs of epinephrine toxicity—indigestion, panic states, tremor, hyperglycemia—and was difficult to rule out before the introduction of sympatholytic agents such as benzodioxane to inhibit and histamine to provoke the pressor phenomenon. Removal of the tumor cures the disorder, although in some older subjects benign hypertension may persist.

**Adrenal Cortex.** Hypertension may be evoked, even in children, by very high sodium chloride intake—30 Gm. daily, or more. It occurs in normal people or those with Addison's disease treated with high dosage of desoxycorticosterone. This is a synthetic product, and its natural analog is not detected in blood or urine, either in health or in disease. Heart failure occurs early in desoxycorticosterone poisoning, and all the symptoms and the hypertension can be prevented if sodium ingestion is stopped during drug therapy. It is tempting to speculate whether cases of benign hypertension with early onset of edema and heart failure may be due to hyperadrenocortical activity of this sort, without other cortical dysfunction. This is of particular interest in cases having thick adrenal cortices, or those which are exquisitely sensitive to sodium restriction. In acromegaly and in Cushing's syndrome there is also a hypertension which may be due to adrenal dysfunction. Here too the vasomotor center seems to play an important role in the syndrome. In acromegaly the adrenal cortex is not thickened, as it is in Cushing's syndrome, and there is no proof of the existence of a cortical hypertension. Nor has the mechanism of hypertension in desoxycorticosterone overdosage been elucidated. The usual lag after treatment begins, before the pressure rises, is 10 to 20 days.

In congestive heart failure, and in mitral stenosis without failure, a rise in arterial pressure is often noted. In failure this may drop to normal as soon as effective therapy is under way. The mechanism is unknown, but in congestive failure it seems probable that the desoxycorticosterone-like hormonal activity is augmented.

## RENAL HYPERTENSION

In some animals a sharp rise in arterial pressure occurs if the renal artery is released after many minutes of occlusion. In nearly all mammals constriction of the arteries supplying all renal tissue, and in some species even constriction of vessels to half the renal tissue, causes hypertension. Wrapping the kidneys in silk or cellulose, and regeneration of renal stumps after subtotal nephrectomy, also leads to hypertension. When hypertension is effected by manipulating only one kidney, it usually clears up when the kidney is removed, if the disorder has lasted only a few days or weeks; it may persist if the disorder has been present for months before removing the altered kidney. In the early phase, angiotonin or analogous renal products may be demonstrated and sympatholytic agents cause minimal fall in pressure. In later stages, no such renal product is demonstrable, and sympatholytic dioxanes may markedly lower pressure.

Vascular lesions may occur in the hypertensive animals, and the evolution of cholesterol atherosclerosis in rabbits is greatly accelerated. The blood flow to the skin, viscera, and muscles is normal in experimental renal hypertension, and the renal vein blood is not anoxic. Intense arterial anoxia, from breathing air poor in oxygen, does not affect renal blood flow or arterial pressure in animals or men.

It may be concluded that humoral substances liberated or withheld by kidneys with poor pulsation, either in the renal artery or in the organ as a whole, cause a rise in vascular tone and probably also a rise in tone of the vasomotor center. With the passage of time the process may become irreversible, but whether this is due to changes in the opposite kidney or in the vasomotor center is unknown. Sensitization to epinephrine is also present in renal hypertension, and the development of the condition is greatly accelerated, in some types of renal injury, by high salt intake, or by desoxycorticosterone with adequate sodium ingestion.

If Acute renal hypertension is observed in man under various conditions, including toxemia of pregnancy, hemorrhagic nephritis, and in anurias due to lower nephron damage. This is sometimes very sensitive to the balance of sodium intake and loss; it predisposes to heart failure and to cerebral edema with convulsions, and is not correlated closely with the degree of urea retention. The part played by the vasomotor center and by the renal pressor substances acting in the periphery has not been established, but the vasomotor element is large, for flow in the arm, on blocking the nerve with cocaine, rises to higher levels than in normal subjects or in the same subject on recovery. The nature and origin of the renal hormone which raises vasoconstrictor tone in these situations, or holds it down under normal conditions, are unknown.

The occurrence of sustained hypertension due to cysts, scars, or vascular lesions in one or both kidneys led to the study of renal hypertension. In amyloid disease, normal blood pressures with severe renal lesions are more frequent than hypertension. In chronic pyelonephritis, uremia may gradually develop without hypertension, but in most chronic renal disease, with loss of substance and vascular damage, hypertension is marked. In coarctation of the aorta, renal pulsation is reduced and the rise in pressure may be of renal origin. In coarctation the hypertension usually disappears at once if the aorta is resilient enough to permit surgical correction. This makes it seem probable that the frequent failure to correct hypertension when unilateral renal disease is treated by nephrectomy is due to changes in the remaining kidney, and not to permanent change in the vasomotor center. In coarctation the kidneys are protected from the high pressures and their vessels remain normal when those of the retina show advanced disease. In most cases of initially benign, nonrenal hypertension, retinal and renal vascular damage proceed at about the same pace.

In chronic renal hypertension there may be a fall of arterial pressure on sympathectomy, or on giving sympatholytic agents, but this is not regularly demonstrable. No circulating vasoconstrictor agent, or potentiating agent, has been demonstrated. On nerve block the blood flow in a limb rises to the same degree as in a normal individual; it does not rise above this as it does in acute cases. Apparently the vascular bed has

undergone trophic changes and on maximal vasoconstriction permits, at the high level of systemic pressure, the same flow that normal subjects have at a lower pressure.

A considerable group of renal hypertensive cases, and those with the most critical difficulties, are those whose pressures rose before any renal lesion was demonstrable, but whose retinal, renal, adrenal, and pancreatic arterioles have begun to show extensive change, after years or even decades of benign hypertension. Here a renal organic element has been added to the initial functional defect. These cases are called "malignant sclerosis" or "malignant hypertension".

The cardinal criteria of malignant hypertension are, therefore, a fixed and marked elevation of diastolic blood pressure, the presence of striking and progressive alterations in the retina (which reflect corresponding damage in the renal vessels), and steady decline in renal function. In the individual less than 40 years of age, the course is rapid, and death commonly occurs within a few months of the onset of symptoms. Autopsy reveals a slightly enlarged kidney with focal hemorrhages and necrotizing arteriolitis (malignant nephrosclerosis). In older persons, and sometimes in the younger ones, the course is less rapid, even lasting for several years. In these cases of so-called benign nephrosclerosis, the kidney is contracted and the vessels reveal predominantly proliferative rather than necrotic changes. To the clinician, both groups of cases represent malignant hypertension, differing only in the rate of evolution of the process.

In many types of chronic renal disease, renal arteriosclerosis, along with retinal sclerosis, develops during the disease. In all cases of hypertension with retinal disease, some remissions in progress of visible vascular retinal lesions may occur with no fall in blood pressure, but such remissions, with recovery of vision, are far more frequent in cases where the pressure level falls, either because of treatment or in connection with intercurrent disease such as myocardial infarction or apoplexy. Remissions due to any type of therapy are less frequent in renal hypertension than in the benign disorder. Except for renal failure with uremia, the symptoms and concomitant disturbances of function are the same in renal as in nonrenal cases. In slowly progressing Bright's disease, asymptomatic hypertension may be present for several decades, and the ter-

final episode may be due to heart failure or coronary occlusion while the retina is still sound.

### STUDY OF HYPERTENSIVE PATIENTS AND MANAGEMENT OF HYPERTENSION

In evaluating the situation of a hypertensive patient, one begins with the history of past renal disease, the presence and usual course of the disease in his relatives, and the nature of his own disability (or lack of symptoms). But, before making intensive inquiry into these matters, the presence of proteinuria, of coarctation (weak late femoral pulse with hard, sharp radial pulse, erosions of ribs in the roentgenogram), or of bulky polycystic kidneys should be considered. Then inquiry may properly be directed into relevant matters, and particularly into calculating the rate at which the disorder is progressing. If a concentrated morning urine specimen has a specific gravity over 1.020, and is free of protein and pus, the odds are that further renal study, no matter how complete, will add nothing of value. In children and even young adults, it is wise to rule out unilateral renal disease by roentgen study. Older patients rarely benefit by nephrectomy, even if the opposite kidney seems functionally normal and the resected one is severely diseased.

If proteinuria or fixed low specific gravity is noted, the case is one of Bright's disease and must be studied to determine degree of creatinine and urea retention, nature of sediment, and size of the kidneys. Where the history is nil, and uremia with retinopathy is present, it may be impossible to determine whether the lesions of the kidney preceded or followed hypertension. The differential diagnosis has little value in prognosis or therapy in such a case, and may not be agreed on by experts in morbid anatomy reviewing the final evidence.

When Bright's disease, polycystic disease, coarctation, and healed pyelonephritis have been eliminated, it remains to rule out adrenal tumor, if necessary, by histamine test and response to sympatholytic agents. Often this can be done by the history of gradual evolution over a period of many years. Evidences of endocrine dysfunction and of early onset of congestive failure may rouse suspicion of adrenal cortical disease; its absence can be proved only by exploration. In connection with sympathectomy for benign hyper-

tension, adrenal tumors have been discovered in over 5 per cent of the cases. Many of these may be incidental, not causative, and in some cases hypertension persists after the nerve section and removal of the tumor.

If hypertension is asymptomatic, the retina healthy, the heart of normal size, and renal function normal, management by skillful neglect and reassurance is permissible. When the patient has vague symptoms but sound organs, sedation and search for causes of frustration and anxiety are in order. Heart failure and uremia are managed conventionally in the hypertensive patient, but certainly the former indicates the need for more drastic efforts to lower the pressure. Even those most skeptical of the relation of hypertension to vascular disease concede that, if the load is reduced, the heart does better. In any event, the personalities of patient and physician, as well as the findings and story, greatly alter the mode of treating, or neglecting to treat, this disorder.

The author believes that hypertension hastens vascular disease and predisposes to catastrophes in the cerebral, retinal, and coronary arteries, as well as to renal failure and heart failure. Neglect of therapy is justified only if the patient is made worse, or likely to be made worse, by emphasizing the hazards of his condition and, therefore, the need for unpleasant therapeutic intervention. Since the psychogenic factor is great, consideration of the abatement of causes of unrest, including dread of disease and of therapy, come high in the list of considerations as to alternative managements. It may be best to begin with mild phenobarbital sedation and restricted use of salt, later proceeding to trial of salt depletion, and finally to sympathectomy, if the rate of progress of symptoms and signs warrants a procedure with a definite postoperative morbidity and disability even if successful. Rigid salt elimination is most effective for headache, dizziness, and heart failure, but does reduce pressure in a significant percentage of the early cases. It must be modified at once if the blood urea begins to rise, as it may precipitate fatal uremia when renal function becomes impaired.

Specific drug therapy, with veratrine, tetraethylammonium, and other agents is too hazardous and too rarely effective to be used for routine management. Thiocyanate must be regarded as a special sedative, to be used with caution or not at all, rather than as a specific. Indeed, there is

no specific therapy for hypertension, only management for the situation existing, at any given time, in each patient with this symptom of circulatory abnormality.

In evaluating therapeutic measures, greater significance should be attached to a decline in blood pressure as determined in the recumbent posture indicating a real decrease in peripheral resistance, than to a similar decline occurring only

in the sitting posture and indicating a tendency toward postural hypotension.

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## Circulatory Failure

T. R. Harrison

### Clinical Pictures of the General Circulatory Disturbances

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Disturbances of the circulation may be either local in one part of the vascular bed, or general and accompanied by an over-all change in circulatory dynamics. The local disturbances produce disorders of function of the part involved, and are considered elsewhere (especially Chapters 3, 242, and 236). The three cardinal types of general circulatory disturbances are characterized by absolute or relative changes in cardiac output. One of these which may be designated by the unsatisfactory term "overactive heart" is accompanied by an increase per unit of time. The other two cardinal circulatory disturbances represent types of circulatory failure which may be defined as a state in which there is an absolute or relative decline in the minute cardiac output. (The important question as to what is meant by "relative decline" will be considered later.)

### CLINICAL PICTURES OF THE GENERAL CIRCULATORY DISTURBANCES

The state, which for want of a better term is called the "overactive heart," is the result of increased cardiac output per unit of time. Subjectively, palpitation is likely to be the dominant complaint. Objectively, the heart sounds are loud, functional systolic murmurs (at the apex and especially at the pulmonary area) are frequent, the pulse is full and bounding, and the pulse pressure tends to be elevated. The objective circulatory phenomena of this condition, therefore, tend to mimic lesions of the mitral valve in so far as examination of the heart is concerned, and tend to mimic aortic insufficiency in so far as the peripheral vascular bed is concerned.

The manifestations of the overactive heart may be seen in normal subjects under conditions of exercise or emotional stress. They appear in a diverse group of diseases of which thyrotoxicosis, outspoken anemia, arteriovenous fistula, Paget's disease, beriberi, and conditions associated with fever or anoxia are the most important. In some of these disorders the circulatory disturbances may dominate the clinical picture and mask the underlying disease.

The clinical manifestations of *peripheral circulatory failure* vary, depending on the severity of the condition and the acuteness with which it develops. Apathy and lassitude are the earliest manifestations when the condition develops slowly over a period of several hours; faintness and syncope when it occurs acutely; sudden death may occur when there is massive hemorrhage. When forward failure is outspoken, the blood pressure declines, the systolic being reduced before the diastolic. Reduction of pulse pressure is, therefore, one of the earlier objective manifestations. The skin is either cold and clammy or dry and inelastic. Other features of the clinical picture will be discussed later.

The clinical manifestations of ~~chronic congestive heart failure~~ vary according to the side of the heart initially affected. This is the left in most cases, and consequently the earliest manifestations are usually those of pulmonary congestion—i.e., dyspnea, orthopnea, rales at the lung bases (when pulmonary edema exists), cough, reduction of vital capacity, prolongation of the pulmonary circulation time, and increased vascular markings in the roentgenographic lung fields. When right-sided failure supervenes, the veins become distended, the systemic venous pressure rises, and the liver becomes engorged. Edema is usually found in persons with right-sided heart failure; its relationship to the elevation of venous pressure, and to other factors, such as increase in total blood volume, will be considered later. Right-sided failure is usually the result of pulmonary hypertension consequent either to left-sided failure or to pulmonary disease. Occasionally it sets in acutely, as in certain instances of pulmonary embolism or of myocardial infarction.

Since most of the underlying causes of heart disease are of such a nature as to place the primary strain on the left side of the heart, it is common to observe the manifestations of left-sided heart-failure in the absence of those of right-sided failure. Most patients presenting the latter phenomena will also have evidence of left-sided failure, because the rise in pulmonary pressure consequent to left-sided failure is the usual cause of right-sided failure.

~~Acute heart failure~~ is of two main types. One of these is ~~acute pulmonary edema~~. This condition is characterized by the sudden onset of severe dyspnea which usually awakens the patient from

a sound sleep. Moist rales appear, first at the lung bases and then throughout the lungs. The face, at first usually florid, becomes cyanotic as arterial anoxia occurs. Cough is prominent and at first unproductive, but later there is expectoration of copious, frothy, pinkish sputum. Wheezing may be pronounced (cardiac asthma). The cervical veins may be distended. The pulse tends to be full and bounding but may become feeble and "thready" in the terminal stages of a fatal attack. ~~X~~ The other type of acute heart failure produces a clinical picture which resembles closely that of peripheral failure but, in addition, some phenomena of congestion are present. When these arise in the lungs, dyspnea, orthopnea, and rales may be found; when the systemic circulation is affected, the veins are distended. In many instances inspection of the veins will allow one to decide immediately whether the heart or the periphery is primarily concerned.

Before considering the various mechanisms whereby these several clinical pictures are induced, it is necessary that certain concepts of the normal and abnormal physiology of the circulation be reviewed.

## GENERAL PRINCIPLES

Figure 24 illustrates that the volume of liquid flowing through a tube will tend to vary with the fourth power of its radius, and with the first power of the difference in pressure. It is, therefore, evident that the inflow of blood into the ventricle during diastole will depend not only on the cross-sectional size of the great veins and on the central venous pressure, but also on the ventricular diastolic pressure which constitutes an impediment to inflow. More complete emptying of the ventricle, whether due to decline in peripheral resistance or to increase in contractile power, will lower ventricular diastolic pressure and hence tend to increase inflow and output. Conversely, less complete emptying of the ventricle will tend to reduce inflow and output.

Before considering the complex circulation of the intact organism, it may be well to attempt to apply the hydrodynamic considerations mentioned in the previous paragraph to the circumstances prevailing in the heart-lung preparation. Here, the peripheral circulatory system is excluded and neurogenic influences on the heart

are absent. In this preparation the right side of the heart is filled from a venous reservoir, which can be set at any desired level. After passing through the lungs and the left side of the heart, the blood flows through an artificial resistance which can be varied at will to alter arterial pressure. From this periphery the blood returns to the venous reservoir.

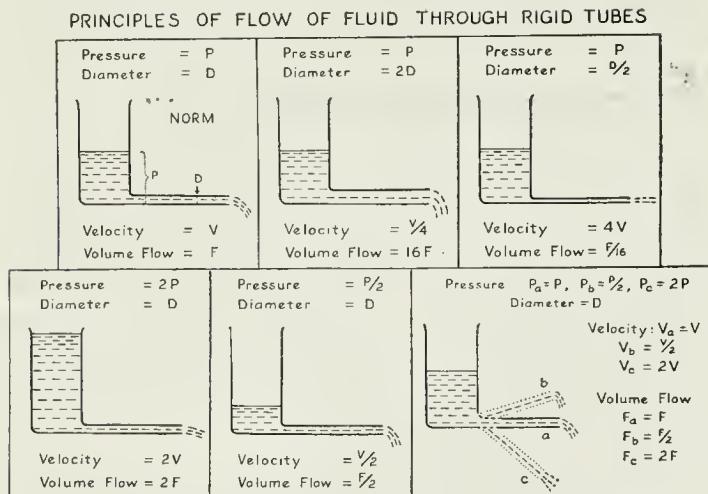


FIG. 24. The purpose of the figure is to illustrate the hydrodynamic principles involved in the filling of the heart. The simple conditions existing in a rigid system with capillary tubes and constant movement do not apply quantitatively to the beating heart and expansile veins. But the general principles are applicable in a qualitative sense. It is clear that, with constant duration of diastole, the three factors which will determine the inflow into the heart are (1) the mean pressure existing in the great veins; (2) the mean atrial and ventricular diastolic pressures; and (3) the cross-sectional diameter of the great veins. The latter factor is especially important, and a relatively small change in it will cause a marked change in flow, under constant conditions of pressure. A rise in the pressure in the ventricle will tend to inhibit ventricular filling if venous pressure and cross-sectional diameter remain constant.

Another point illustrated by the diagram is that the volume of flow and the velocity of flow may vary in the same direction (when the pressure varies and the diameter of the vessels remains constant) or in opposite directions (when the diameter varies and the pressure remains constant).

Studies with the heart-lung preparation have shown that the normal response of the heart to augmented load (produced either by increasing the peripheral resistance or by raising the venous reservoir) is temporary decrease in output as compared to inflow, with consequent dilatation. The increase in length of the fibers at the onset of the succeeding systole causes a greater release of energy. When the degree of dilatation is not too great, a normal fraction of the energy is transformed into work and the mechanical efficiency remains at a high level. When dilatation is ex-

cessive, the mechanical efficiency declines, and the amount of work performed diminishes even at the high level of energy expenditure.

If, in the heart-lung preparation, the level of the venous reservoir is lowered, the diastolic filling of the heart is reduced and the systolic output declines. If the lowering of the venous reservoir is of sufficient degree, filling and output diminish so much that coronary circulation becomes inadequate to supply the needs of the heart, which soon ceases to beat. Under such circumstances we are dealing with failure of the preparation, not as the result of a disorder of the heart but as the result of a defective venous return (inflow load). It will be pointed out later that this set of circumstances corresponds to peripheral circulatory failure in man.

If the venous reservoir is raised, different consequences ensue. The filling and output of the heart increase. As the level of the reservoir is progressively raised, a time comes when the increment of output becomes progressively less with increasing increment of the reservoir level. Eventually, further rise in the filling load causes no further increase in output, and when this point is passed a still further elevation of the venous reservoir causes a decline in output (fig. 25). Under such circumstances the heart is markedly distended during diastole, but empties itself ineffectively in systole. The residual blood at the end of systole is therefore markedly increased.

In the following discussion there will be repeated references to the Starling curve. When the heart is stated to be on the left or ascending limb of the curve, it will be understood to be in a state in which a further rise in venous load will cause some increase in output. Conversely, the expression that the heart is on the right or descending limb of the curve indicates that rise in filling load will produce decline in output. (The simplicity of the concept seems to justify such unconventional use of the word "on.")

Interpretation of what happens under the conditions of increasing venous load may perhaps be aided by a consideration of the hydrodynamic principles illustrated in figure 24. Since in the heart-lung preparation the size of the central venous stream bed remains essentially constant, it is

clear that the filling of the heart during diastole will depend on the difference between the pressure in the venous reservoir and in the ventricle. During the early stages of elevation of the venous reservoir, the filling readily keeps pace with the progressive elevation, indicating that there is no

THE STARLING CURVE IN RELATION TO THE STAGES OF HEART-FAILURE

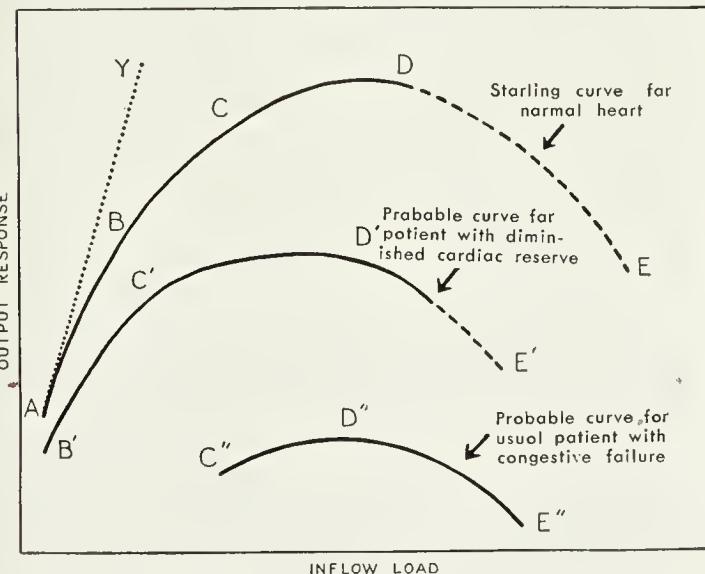


FIG. 25. This figure is diagrammatic and not strictly quantitative. The curve A-Y represents the theoretic output response of a perfect machine to progressive increase in inflow load. The curve A-E represents the effect of increasing inflow load on the cardiac output of the heart-lung preparation. When transferred to men performing exercise, it appears probable that only the solid portion A-D applies to normal subjects, and to persons with asymptomatic heart disease. In such persons muscular exhaustion would probably cause cessation of exercise before the cardiac output would begin to decline (dotted line).

The curve B'-E' represents the probable state of a patient with cardiac disease showing no symptoms at rest, but showing dyspnea on exertion. At rest the cardiac output is somewhat reduced but the inflow load is normal. With muscular exercise the cardiac output shows a less sharp rise in response to the increasing inflow load, and tends to decline when the inflow load becomes great.

The curve C''-E'' indicates the state of a patient with severe congestive failure. Even at rest, the inflow load is very high, while the cardiac output is somewhat reduced. Exercise causes only a slight increase in cardiac output, followed by a decline. In the case of a patient with congestive failure of the high-output type, this curve would be at a higher level but would have the same shape.

impairment to filling, or, in other words, that the ventricular diastolic pressure is not elevated. However, when the filling during each diastole becomes progressively less, and finally declines as the reservoir is further elevated, it becomes clear that the cause is hindrance to filling in the ventricle as the result of elevation of ventricular diastolic pressure. Such elevation can come about

only as the result of accumulation of residual blood in the ventricles. Such residual blood can accumulate only because the systolic emptying is less complete than before. A condition has, therefore, been reached in which the stroke volume, although elevated (fig. 25), is still not adequate to cause sufficient emptying of the ventricle during systole to eliminate residual blood, and to prevent a rise in ventricular diastolic pressure. Hence, inflow is hindered during the succeeding diastole.

The sequence of events just described corresponds to the clinical state known as "high-output failure," or "heart failure due to primary increase in inflow load," and is discussed later.

Another way in which heart failure may be produced in the heart-lung preparation is by a marked increase in the peripheral resistance, the level of the venous reservoir remaining constant. As the resistance is increased, the heart responds during the first few beats with diminished emptying. Since the reservoir level is constant, the filling temporarily exceeds the emptying and the ventricle dilates. The dilated ventricular musculature is able to release more energy, and the systolic discharge tends to increase. Shortly, a new equilibrium is established with the stroke volume at the original level but with greater diastolic and systolic volumes. Further increase in peripheral resistance has similar effects, the heart dilating each time but the stroke volume tending to return to the previous level. However, with still further increase in peripheral resistance, the load becomes so great that ventricular discharge is seriously hampered, and sufficient residual blood accumulates in the heart to cause a well-marked rise in ventricular diastolic pressure. The difference between the venous (i.e., reservoir) pressure and the ventricular diastolic pressure is therefore reduced, and inflow diminishes. The new equilibrium is now established at a lower level of cardiac output. This, in turn, can be overcome by raising the venous reservoir so that the effective difference between venous pressure and ventricular diastolic pressure is reestablished. Under these conditions the inflow per beat and the output may return to normal, but only at the expense of still further dilatation of the heart, and still further energy expended per beat. If the artificial peripheral resistance be increased still more, a time eventually comes when the heart is at the

top of the Starling curve (fig. 25) functionally, and when further increase in the level of the venous reservoir will cause a decline in output, the heart beat soon ceasing unless the resistance is reduced.

The situation just described indicates how mechanical factors which force the heart to empty against greater resistance may cause heart failure even though the muscle is essentially healthy. Under these circumstances the cardiac output tends to be low, but may be normal if the venous load is high. The circumstances described are analogous in many respects to heart failure resulting from aortic stenosis, or from hypertension without myocardial disorders other than hypertrophy and dilatation.

In the heart-lung preparation, failure may be produced by still other procedures. Certain drugs which injure the myocardium may be employed, or the heart may be allowed to beat for a number of hours, during which time spontaneous decline in the functional capacity of the myocardium occurs. If, under such circumstances, the venous reservoir and the peripheral resistance are kept constant, the deterioration of the myocardium is indicated by reduced systolic emptying. When this process first begins, the filling goes on at approximately the same rate as before. Hence the heart receives, for a few beats, more blood than it expels, and the ventricles dilate. If the capacity of the myocardium is not too much impaired, the increased length of the fibers allows the heart to expel more blood and the systolic output tends to return to the previous level, this restoration being purchased at the expense of a lasting increase in systolic and diastolic volumes, and of increased energy expenditure. The mechanical work performed by the heart is now the same as it was in the beginning, because the pressure against which the blood is expelled has remained constant, and the output has been restored to the initial level. The situation is, therefore, one in which a given performance of work can be obtained only at the expense of increased energy expenditure—i.e., a situation in which there is a diminished mechanical efficiency of the heart. Such a decline in mechanical efficiency is believed by many to be a characteristic feature of heart failure resulting from deterioration of myocardial capacity. Others hold that an actual decline in work done is the more important feature.

As the strength of the myocardium decreases further, the venous reservoir and peripheral resistance remaining constant, the events described continue to proceed, the systolic emptying becoming less complete, and being restored by dilatation consequent to incomplete emptying with residual blood. After a time, however, the ventricular diastolic pressure begins to undergo significant rise, and when this occurs the venous filling is less than before. Under such circumstances elevation of the venous reservoir may cause a decline rather than an increase in cardiac output, because the deterioration of myocardial capacity has reached such a point that the heart has now passed over the peak of the Starling curve (fig. 25). This has not been brought about by increased work, as in the previous situations, but by diminished capacity to carry on normal work.

The circumstances just described are comparable to the situation of a patient with heart failure resulting from any condition which impairs the strength of the myocardium.

*To recapitulate:* In the heart-lung preparation the circulation may fail (1) because blood is not supplied to the heart, even though this organ is entirely capable of handling such blood; (2) because the venous load (inflow load) is greater than the heart can tolerate; (3) because the arterial load (i.e., the mechanical resistance to systolic emptying) is excessive; and (4) because there is primary inability of the myocardium to do its work. These several disturbances correspond to certain clinical states.

The principles learned from the heart-lung preparation are of great value in understanding circulatory disorders in man, provided certain limitations are clearly understood. The heart-lung preparation reveals important information concerning the effects of excessive load on the myocardium, and concerning primary disorders of the myocardium. In the patient, heart failure may result not only from such disturbances of the myocardium, but also from primary disorders of the pericardium and the endocardium. Certain other limitations such as the variability of peripheral resistance and the consequent variation in systolic emptying will be considered later.

Conceptions of circulatory failure are clarified when the relationship between venous pressure,

inflow load (i.e., venous load), and output are clearly understood. The output of either ventricle is equal to the inflow except in so far as the amount of residual blood is altered. The inflow depends on a number of factors, of which the most important are the cross-sectional diameter of the central venous stream bed and the mean difference between the pressures in the great veins and in the ventricle during filling. A rise in the ventricular diastolic pressure constitutes an impediment to inflow. The inflow load may, therefore, be defined as the amount of blood offered to the ventricle in diastole or as the inflow which would occur if the ventricular pressure remained at zero throughout diastole. A rise in ventricular diastolic pressure will, therefore, cause a reduction of inflow if the load remains constant. A rise in inflow load will cause increase in actual inflow unless accompanied by a corresponding increase in ventricular diastolic pressure. It will become apparent from the later discussion that "the level of ventricular diastolic pressure tends to be inversely proportional to the reserve power of the heart."

Rise in ventricular diastolic pressure may come about either (1) when the stroke volume declines; (2) when the inflow is so great during diastole that despite an increased stroke volume during the succeeding systole the ventricle fails to empty adequately; (3) when there is mechanical hindrance to ventricular filling as the result of pericardial disorders.

In the intact animal an increase in atrial pressure will tend, on the one hand, to increase flow into the ventricle, and, on the other hand, to decrease flow from the veins. Similarly, increased pressure in the veins will tend to increase flow into the atrium, but to depress flow from the capillaries. (Obviously, such depression will soon be partially overcome, for secondary rise in capillary pressure and in the size of the venous stream bed will tend to reestablish the previous level of flow.) Because of the absence of a peripheral circulation and capillary bed, the second effect is absent in the heart-lung preparation, and within the physiologic range, the only effect of a rise in venous pressure will be to increase output.

It seems probable that normal subjects may display well-marked alterations in the size of the stream bed of the great veins as the result of distributional shifts in blood volume consequent to alterations in venous and arterial tone. Such alterations, the changes in intrathoracic pressure

consequent to respiration, and alterations in ventricular diastolic pressure secondary to changes in peripheral resistance, and hence in stroke volume, probably account for the lack of parallelism in healthy subjects, between cardiac output and venous pressure.

In the intact organism the movement of blood proceeds in a closed circle. Hence it is not only true that output depends on inflow, but also that inflow depends on output. The amount of blood returned to the right ventricle cannot exceed, over any long period of time, the amount of blood expelled by the left ventricle. The inflow and the output are therefore interdependent. Either an increase in myocardial strength or a decline in peripheral resistance will tend to increase systolic emptying which will lower ventricular diastolic pressure and produce increased inflow if venous pressure and cross-sectional diameter of the great veins remain constant. Under most circumstances it appears that alterations in output are secondary to changes in inflow. A common example is change in posture. When the ~~recumbent position~~ is assumed, blood moves centrally from the dependent portions, the size of the central venous stream bed increases, inflow load rises, and output increases. The reverse changes occur when the subject stands.

The foregoing discussion may be summarized by stating that the intact animal differs from the heart-lung preparation in that in the latter the venous pressure tends to furnish an accurate index of inflow load, while in the former no such relationship necessarily exists. However, all of the evidence indicates that in both instances the Starling principle applies in that output depends on inflow, and that the actual inflow depends on the inflow load (central venous stream bed size and venous pressure) minus the impediment to inflow offered by the ventricular diastolic pressure.

## CLASSIFICATION OF CIRCULATORY DISTURBANCES

These disorders may be classified in several different ways:

### I. TOPOGRAPHIC CLASSIFICATION

(According to structure initially affected)

A. *Disturbances arising primarily in the periphery:*

- 1. "Overactive heart"
- 2. Peripheral circulatory failure (including various subgroups as indicated later)
- B. Disturbances arising primarily in the heart:
  - 1. Myocardial
  - 2. Pericardial
  - 3. Endocardial

Since there are certain differences in the mechanism of heart failure produced by myocardial, pericardial, and endocardial disorders, respectively, this classification has certain advantages. Its disadvantage as a sole classification becomes apparent when it is compared with the classifications to follow.

## II. CLINICAL CLASSIFICATION

(According to clinical pictures)

- A. "Overactive heart"
- B. Shocklike state:
  - 1. Without coexisting evidence of congestion (peripheral circulatory failure)
  - 2. With coexisting (but usually minimal) evidence of congestion (most types of acute heart failure):
    - a. Asystole
    - b. Cardiac syncope
    - c. Cardiac collapse
- C. Congestive failure:
  - 1. Acute pulmonary edema
  - 2. Chronic congestive failure:
    - a. Left-sided
    - b. Right-sided
    - c. Combined

The clinical classification has practical value but does not convey an adequate understanding of the important mechanisms involved in the different types of circulatory failure.

## III. FUNCTIONAL CLASSIFICATION

(According to initiating mechanism)

- A. Primary increase in inflow load (with adequate systolic emptying): Subgroups as in C-1, below
- B. Primary deficiency of inflow load (peripheral circulatory failure):
  - 1. Primary decline in blood volume (hematogenous type):
    - a. External hemorrhage

- b. Loss of fluid or whole blood into body tissues
- c. Loss of water and electrolytes from gastrointestinal tract, kidneys, etc. (e.g., intestinal obstruction, diabetic coma)
- d. Deficient fluid intake (late stages of acute and chronic water deficit, Chapter 28).
- 2. Primary loss of vascular tone (neurogenic type):
  - a. Vasodepressor syncope (emotional disturbances, hypersensitive carotid sinus, etc.)
  - b. Injury to nervous system:
    - (1) Physical (disease of spinal cord, section of sympathetic nerves)
    - (2) Chemical (spinal anesthesia)
  - c. Venous pooling:
    - (1) Defective postural venoconstrictor reflex
    - (2) Varicose veins
    - (3) Atonic musculature
- 3. Primary arteriolar and/or capillary dilatation (vasogenic type):
  - a. Administration of certain drugs (histamine, nitrites)
  - b. Liberation of histamine-like substances in injured tissue
- 4. Mixed types of peripheral failure
- C. Excessive inflow load in relation to systolic discharge (heart failure):
  - 1. Primary increase of inflow load (with secondary inadequacy of systolic emptying):
    - a. Disordered tissue oxidative processes (thyrotoxicosis, anemia, beriberi)
    - b. Arteriovenous communications
    - c. Primary hypervolemic heart failure:
      - (1) Spontaneous: Acute pulmonary edema, acute nephritis
      - (2) Induced: Excessive administration of fluids, desoxycorticosterone intoxication
  - 2. Primary decline in cardiac output (with secondary rise in inflow load):
    - a. Increased peripheral resistance:
      - (1) Acute (e.g., massive pulmonary embolism)
      - (2) Chronic (e.g., hypertension)
    - b. Acute disturbances of the myocardium (without secondary hypervolemia):
      - (1) Primary disorders of rate and rhythm:

- (a) Ventricular asystole (fibrillation or standstill)
- (b) Sudden bradycardia (myogenic and neurogenic)
- (c) Ectopic tachycardias
- (2) Acute myocardial disease
- c. Chronic myocardial failure (with secondary hypervolemia)
- 3. Primary mechanical interference with ventricular filling (with secondary increase in inflow load and decline in stroke volume):
  - a. Tamponade due to thickening of pericardium or fluid in pericardium
  - b. Stenosis of auriculoventricular valves

In all of these types of heart failure the atrial pressure tends to be elevated, and in all except the last mentioned the ventricular diastolic pressure tends to be elevated.

Each of these classifications has advantages and disadvantages. In the discussion to follow, certain features of each will be utilized, but the main trend of thought will be along the lines of the functional classification.

It should be noted that the functional approach to circulatory failure permits logical integration between the events in patients and those in the heart-lung preparation. Thus "primary deficiency of inflow load" (peripheral failure) corresponds to the state induced by excessive lowering of the venous reservoir, while "primary increase in inflow load" ("overactive heart") corresponds to the state induced by moderate elevation of the venous reservoir. Heart failure due to primary increase in inflow load ("high-output failure") corresponds to the dynamics of the heart-lung preparation when the venous reservoir is raised excessively. Heart failure due to increase in peripheral resistance is similar, clinically, to that in the heart-lung preparation, while heart failure due to primary disorders of the myocardium resembles that which occurs as spontaneous fatigue develops in the heart-lung preparation.

Of these various types of circulatory failure the peripheral type is the most common and important. However, since its mechanisms seem to be reasonably clear, most of the discussion to follow will deal with heart failure about which wide (and healthy) differences of opinion exist at the

present time. Throughout the discussion of heart failure, emphasis will be placed upon the primary hemodynamic changes which are related to the heart itself. Secondary alterations, such as dyspnea and edema, which result from the heart failure will be discussed only briefly, as they are considered in detail in other chapters.

## THE OVERACTIVE HEART

(Primary increase of inflow load)

The venous return to the heart may be increased under a number of circumstances. Physiologically, this occurs during muscular exercise. Various disorders which lead to disturbances of oxidation in the tissues are common causes. Among these are arterial anoxia, severe anemia, thyrotoxicosis, and excessive elevation of body temperature. In these conditions there is probably accumulation of metabolites in the tissues as the result of lowered oxygen tension. Even when the oxygen tension is not reduced, similar metabolic dislocations can apparently be caused by disturbances in enzyme systems as the result of deficiencies of certain substances, of which thiamin is apparently the most important. These several metabolic disturbances lead to vasomotor adjustments such as decline in peripheral resistance with consequent increase in peripheral blood flow and in venous return to the heart. A similar mechanical effect is produced by arteriovenous communications.

**II** Hypervolemia occurs during normal pregnancy and in a number of abnormal states. It probably occurs in acute nephritis, although this does not seem to have been established beyond question. It may appear temporarily when edema fluid is rapidly reabsorbed into the blood stream. It may be induced by the administration of excessive quantities of fluids or of large doses of desoxycorticosterone, with consequent retention of sodium and water. Increase in the circulating blood volume leads to increase in the size of the vascular bed, including the central venous stream bed. It may also lead to increase in venous pressure, especially when the hypervolemia develops rapidly.

Regardless of whether the primary disturbance is tissue oxidation, arteriovenous shunt, or hypervolemia, the inflow load increases, and at the same time decline in peripheral resistance tends to make systolic emptying more complete and to

lower ventricular diastolic pressure. The resulting increase in cardiac output produces a characteristic clinical picture of which moderate tachycardia, exaggerated intensity of the heart sounds, functional systolic murmurs, increased peripheral pulsations, bounding pulse, and elevation of pulse pressure are the most important features.

As long as the heart is able to meet the load by adequate systolic emptying, heart failure does not develop. However, when the load is sufficiently excessive or when the reserve power of the heart is sufficiently impaired, the emptying fails to keep pace with the inflow, ventricular diastolic pressure rises, and the manifestations of heart failure appear. This type of heart failure will be discussed later, but it should be emphasized here that the peripheral resistance is a factor of great importance in determining whether increase in inflow load will cause heart failure. Thus heart failure is rare in young patients with thyrotoxicosis (decreased peripheral resistance) but is common in young patients with acute nephritis (increased peripheral resistance).

### PERIPHERAL CIRCULATORY FAILURE

(Primary decrease of inflow load)

Peripheral failure is to be sharply distinguished from heart failure, from which it differs as regards cause, mechanism, and management.

Regardless of its underlying cause and outstanding clinical picture, the immediate mechanism responsible for peripheral failure is decline in inflow load, leading to decrease in cardiac output, and hence to inadequacy of the blood flow to the tissues. When the onset is sudden, there is no time for compensatory adjustments to occur and the brain suffers severely—hence consciousness is lost. When the onset is more gradual, compensatory adjustment in the form of vasoconstriction in the less vital areas occurs, the cerebral blood flow is kept at a more nearly normal level, and, in the absence of other complicating factors, consciousness is usually retained.

Peripheral circulatory failure may be subdivided into several types, according to which of the various functions is initially disturbed.

**1. Primary decline in blood volume** may be brought about by hemorrhage, by loss of fluid or whole blood into injured tissues (traumatic

shock, burns, etc.), or by the development of a deficit in extracellular fluid volume as the result of reduced water intake or excessive loss of water and electrolytes from the gastrointestinal tract, kidneys, or skin. This is the most serious and important type of peripheral circulatory failure, and it is in this type that replacement therapy, utilizing blood, plasma, electrolytes; or water (depending on the nature of the deficit) has its greatest value, while vasoconstrictor drugs are relatively useless.

**2. Primary loss of vascular tone** may occur as the result of emotional disturbances (psychogenic syncope, Chapter 7), of physical insults (i.e., transection of the spinal cord), or of chemical injury (e.g., spinal anesthesia) to the nervous system. Various diseases of the spinal cord may interfere with the postural vasoconstrictor reflex and cause syncope on standing. In such instances the decline in blood pressure is primary, and hence vasoconstrictor drugs may be of great temporary value.

**Venous pooling** likewise may lead to peripheral circulatory failure, and especially when the subject is in the upright position. Such a mechanism is illustrated by the attacks of faintness and syncope in subjects with varicose veins, as well as those which occur while standing still, in persons with atonic muscles. Mechanical measures, such as bandaging the legs, are of especial value in persons with this type of peripheral failure.

**3. Primary arteriolar and capillary dilatation** as the result of chemical agents acting directly on the vessels is probably rare. It may be produced experimentally by the administration of histamine or of nitrates, and is possibly involved in the mechanism of anaphylactic shock. There is some evidence that substances having a histamine-like action may arise in injured tissues and cause local capillary damage, thereby aggravating the reduction in blood volume which is the usual initiating factor in traumatic shock.

From the practical standpoint, it should be emphasized that emotional syncope is the most frequent of the less serious types of peripheral circulatory failure, while primary decline in blood volume is much the most common of the more serious types. The therapeutic implications are obvious.

**4. Mixed Types of Peripheral Circulatory Failure.** In certain patients more than one of these several mechanisms may be active. Thus the soldier struck by a bullet may fall to the ground ("primary shock") as the result of reflex decline in blood pressure, recover temporarily, and then develop progressive circulatory failure ("secondary shock") as the result of internal hemorrhage. Similarly, the individual with acute peritonitis resulting from perforation of a peptic ulcer may have initial reflex general vascular dilatation, later complicated by further local dilatation due to the irritating effect of the gastrointestinal secretions, and eventual decline of blood volume consequent to the escape of water, salts, and protein into the peritoneal cavity. Likewise, multiple mechanisms are probably concerned in the poorly understood circulatory failure occurring in infectious disease. Here the question of adrenal cortical deficiency may have important therapeutic implications. The presence of a normal value for the total (not differential) count of eosinophil cells in the blood constitutes suggestive evidence that adrenal cortical deficiency may be involved in circulatory failure.

The several conditions which have been mentioned all lead to a decrease in blood flow to the peripheral tissues as the result of decline in cardiac output and blood pressure. When such a diminution is of sufficient duration and severity, grave consequences ensue. Impairment of oxidative mechanisms and of enzyme systems may develop. The decline in renal blood flow induces a functional renal insufficiency which may reach fatal proportions. The diminished coronary blood flow may eventually lead to cardiac failure as manifested by gallop rhythm, dilatation, dyspnea, rales, and terminal elevation of venous pressure. In the final moribund stage, vasoconstriction may give way to vasodilatation as the vasomotor mechanisms become impaired, because of prolonged anoxia, which of itself may lead to capillary injury with further escape of fluid from the blood stream. Under such conditions treatment either is entirely unavailing or, at best, offers much less likelihood of improvement. It is, therefore, of cardinal importance that peripheral failure be recognized in its incipient stages when it is readily amenable to therapy, provided the underlying mechanism is clearly understood and managed properly.

## HEART FAILURE

### PRIMARY INCREASE OF INFLOW LOAD BEYOND THE ABILITY OF THE HEART TO RESPOND WITH ADEQUATE SYSTOLIC EMPTYING

(High-output failure)

Certain disorders (disturbances of tissue oxidation, arteriovenous shunts and hypervolemia) which lead to increase in venous return and in cardiac output have already been discussed. Whether such disorders produce heart failure depends on a number of factors, of which the most important are the degree and duration of the load, the reserve power of the heart, and the peripheral resistance. Moderate increase in inflow load, such as occurs during normal pregnancy and in most instances of thyrotoxicosis, may be tolerated for months or years by a healthy heart. On the other hand, a great increase in inflow load may produce failure of a healthy heart within a few days. This is sometimes observed during recovery from burns, when there is vasodilatation and massive reabsorption from the injured tissue of previously administered fluid, and at the same time impaired ability of the kidneys to maintain homeostasis. Even the dog's heart, with its great reserve, may be put into failure in a few minutes by the intravenous administration of very large amounts of colloidal solutions. Many elderly patients, previously free of evidence of cardiac disease, develop failure when given rapid intravenous infusions in comparatively small amounts. The capacity to withstand increased load is impaired by the aging process.

When increased venous load is accompanied by increased arterial load (acute nephritis, desoxycorticosterone intoxication), heart failure tends to occur readily, but when the peripheral resistance is low (thyrotoxicosis, arteriovenous fistula), heart failure may be long delayed.

Of especial interest because of its frequency is acute pulmonary edema, which usually develops in persons with previous congestive failure but may appear in an individual who has never had any symptoms other than moderate dyspnea on effort, indicating diminished cardiac reserve. The attacks occur almost exclusively at night and in persons with disorders such as hypertension or

aortic insufficiency, which put a primary strain on the left side of the heart. It appears that during sleep the recumbent position favors the reabsorption of extracellular fluid accumulated in the dependent portions during the day's activities in the standing or sitting positions. The hypervolemia so induced causes increased inflow load, with consequent rise in the output of the relatively normal right ventricle. The resultant increase in inflow load on the left ventricle is not balanced by a decline in peripheral resistance such as occurs during muscular exercise. Hence the left ventricle, impaired as the result of stress or coronary disease, does not expel completely the increased volume of blood which is now entering it. The left ventricular diastolic pressure therefore rises, with consequent increase in pressure in the left atrium and in the pulmonary vascular bed. Congestion and edema of the lungs therefore develop, especially in the lung bases which are dependent as the result of the supine position. The ensuing labored breathing tends to lower mean intrathoracic pressure, to cause further inflow into the right ventricle, and thereby to create a vicious cycle (Chapter 9).

The clinical picture of heart failure due to primary increase in inflow load is a combination of those pictures already described for the overactive heart and for congestive heart failure.

#### HEART FAILURE DUE TO PRIMARY DECLINE IN CARDIAC OUTPUT

##### HEART FAILURE RESEMBLING PERIPHERAL CIRCULATORY FAILURE

Even though the blood and tissue fluid volumes, the total peripheral resistance, and the venous return suffer no primary impairment, the blood flow through the tissues may become grossly deficient as the result of cardiac failure. When such failure develops slowly, certain secondary mechanisms, of which increase in blood volume is the most important, are set up, and since these usually tend to restore the minute volume of the circulation toward the normal level, the manifestations of collapse remain inconspicuous, while those of congestion are pronounced. However, the story is quite different when cardiac output diminishes suddenly, for under such circumstances there is no time for

secondary mechanisms to come into play, and a clinical picture resembling closely that of peripheral failure supervenes. Even so, the patient with acute heart failure will also display, at an early stage, some of the manifestations (gallop rhythm, cardiac dilatation, dyspnea, rales, venous distention) of congestion; while such manifestations appear either not at all or only in the advanced stages of peripheral circulatory failure, and then are due to cardiac failure which, under such circumstances, may appear secondarily as the result of the prolonged deficiency in coronary blood flow.

**1. Asystole**, due either to fibrillation or standstill of the ventricles, represents the most acute form of forward failure of the heart. It occurs especially in persons with angina pectoris, myocardial infarction, heart block, or extensive and acute myocarditis. Although ventricular fibrillation, once present, is likely to be fatal, its occurrence can sometimes be anticipated and probably prevented by quinidine, which should usually be employed when a patient with one of these several conditions develops numerous ventricular beats, or attacks of ventricular tachycardia.

**2. Cardiac syncope**, due to bradycardia, represents a second form of sudden failure of the heart. The slowing may be either of myogenic (Adams-Stokes syndrome) or neurogenic (reflex) origin. The neurogenic type is usually associated with sinus bradycardia or sinoauricular block, the myogenic type with ventricular standstill or momentary ventricular fibrillation. Similar attacks may occur as the result of ventricular tachycardia. The most common reflex responsible for cardiac syncope is that arising in the carotid sinus, but occasionally the eyes, the alimentary tract, or other tissues may be the source. Syncope attacks of this type, which may often be prevented by atropine, need to be differentiated from those of peripheral origin, which are induced by arteriolar dilatation or by venous pooling, and which are not affected by atropine. Ordinarily, the heart rate serves as an important point of distinction between the cardiac and the peripheral types of syncope. However, the rule that cardiac syncope is associated with bradycardia and peripheral syncope with tachycardia is not without exceptions, for the heart rate is usually reduced in patients with psychogenic (vasovagal) fainting, which has been shown to be

primarily of peripheral origin, and certain patients with paroxysmal tachycardia may develop syncope during their seizures.

**3. Acute cardiac collapse** represents a third type of acute failure of the heart, and is commonly associated with a clinical picture simulating that seen in the hematogenic type of peripheral circulatory failure, but presenting one important point of distinction. In the subject with acute cardiac collapse the coexisting signs of congestion (dilatation, gallop rhythm, labored breathing, rales, venous distention) appear early, while in the patients with peripheral failure such signs are either absent or appear late and in lesser degree.

Acute cardiac collapse may be induced by several different underlying mechanisms, of which the most common is *sudden injury to the myocardium*. **Acute myocardial infarction** represents the classic example, but a similar picture is seen occasionally in subjects with diphtheritic myocarditis or fulminating rheumatic fever, and is less commonly observed in a variety of other disorders which may produce acute myocardial injury.

Another common cause of acute cardiac collapse is **ectopic tachycardia**, whether due to auricular fibrillation, auricular flutter, or paroxysmal tachycardia. In these conditions the mechanical efficiency of the heart is reduced because the output per beat is small. Hence the proportion of the energy expended in raising the intraventricular pressure sufficiently to open the semilunar valves is increased, compared to the proportion used in expelling blood. Furthermore, since the duration of systole is relatively independent of the heart rate, the total duration of systole per minute is increased, and that of diastole correspondingly diminished at rapid heart rates. Since the coronary circulation to the inner part of the left ventricle is normally hampered during systole by the high intramural pressure, any decrease in the total duration of diastole per unit of time tends to reduce the coronary blood flow. Even in persons with structurally normal hearts, tachycardia of sufficient duration and severity may lead to failure, and its baneful effects are magnified when there is preexisting cardiac disease.

A third group of causes of acute cardiac collapse are those in which there is **sudden mechanical hindrance to the action of the heart**. The most

common such conditions are **massive pulmonary embolism** and **acute cardiac tamponade**, the latter being due to the rapid accumulation of blood or serous effusion in the pericardial cavity.

Among the rarer causes are rupture of a valve cusp, of the intraventricular septum, or of a papillary muscle, and occlusion of a stenotic mitral orifice due to a ball-valve thrombus. Such conditions may cause either syncope, collapse, or a combination of these states.

When a patient presenting the picture of collapse is seen, the first problem is the decision as to whether the periphery or the heart is primarily at fault. This decision is made on the basis of the finding of evidence of coexisting congestion. The answer can often be obtained at a glance by inspecting the **cervical veins**. If these are overdistended, the heart usually may be indicted with confidence; if they are abnormally empty, the defect probably, but not necessarily, lies in the periphery. The presence of labored breathing, numerous rales at the lung bases, or excessive alteration in the heart rate (less than 40 or more than 160) speaks for a cardiac origin, while absence of all of these signs points toward a peripheral cause. (These differential points are of greatest value when they are encountered during the earlier stages, for **peripheral circulatory failure, when advanced, may lead to such decline in coronary blood flow as to cause secondary cardiac failure**, attended by labored breathing, rales, and even venous distention.) In both conditions pallor and cyanosis may occur, but predominance of pallor suggests peripheral failure, while predominance of cyanosis suggests cardiac failure. The importance of the presence of arrhythmias, evidence of valvular disease, and cardiac enlargement is obvious; but one should not be misled by such findings into overlooking acute peripheral failure occurring in an individual with preexisting chronic cardiac disease.

#### CHRONIC MYOCARDIAL FAILURE

(The common type of congestive heart failure)

When heart failure sets in acutely, the cardiac output per unit of time is seriously reduced because secondary increase in blood volume, and hence in inflow load, has not had time to occur. Under such circumstances the manifestations of

congestion, while present, are likely to be minimal. When heart failure develops more slowly, a rather different picture occurs, the blood volume and venous stream bed size increasing markedly, the tissue blood flow usually being maintained at a more nearly normal level than in the case of acute heart failure. In such instances the symptoms are mainly the result of engorgement, unless the degree of heart failure is so advanced that the heart is on the right side of the Starling curve (fig. 25), in which case the increase in inflow load produces, not an increase, but a further decline in cardiac output.

It has been pointed out that, in the heart-lung preparation, reduced systolic discharge with consequent accumulation of residual blood and dilatation may be brought about either by excessive arterial resistance or by decline of myocardial capacity. Similar effects occur in patients with such conditions as hypertension and myocardial disease. Regardless of whether the primary disorder affects peripheral resistance or muscle strength, the eventual result tends to be increase in the amount of residual blood at the end of systole, and consequent elevation of ventricular pressure at the onset of diastole. Such elevation tends to hamper atrial emptying, and the atrium tends to accumulate residual blood until the rise in pressure has become great enough to restore in part the difference between atrial and ventricular pressures. The dynamics of ventricular filling may thus be partially reestablished, but only at the expense of a lasting increase in the mean atrial pressure, and of an increase in the volume of blood in the cavities of the heart. However, the rise in atrial pressure induces stasis in the veins and an increase in venous pressure. This is congestive failure.

The sequence of events which has been described may take place on either the right or the left side of the heart. However, it so happens that most of the conditions which cause chronic cardiac disease are of such a nature as to affect the left side, primarily. Therefore, left-sided failure, and consequent congestion of the lungs, commonly appears first. Given a patient with such pulmonary congestion, significant alterations occur in the dynamics of the circulation. The velocity of the flow through the enlarged stream bed is significantly reduced and the circulation time is prolonged. The congested lungs are more rigid and the vital capacity therefore declines.

The shift of blood from the systemic to the pulmonary circuit produces a deficit of blood in the periphery and hence, if prolonged, leads to compensatory increase in total blood volume. It is this increase in blood volume which constitutes the secondary mechanism which not only increases the size of the stream bed but also maintains the high venous (filling) pressure, and hence may keep the cardiac output per minute at a more nearly normal level, with the consequence that the manifestations of collapse are not outspoken.

With a more advanced stage of heart failure the amount of residual blood in the ventricle at the end of systole increases further, and the ventricular diastolic pressure tends to rise to a still higher level. Under these circumstances, even a high level of blood volume and of venous pressure may fail to maintain the cardiac output at an effective level and, as the heart becomes overdistended, a further rise in inflow may cause decline rather than rise in cardiac output. Thus the clinical manifestations of collapse may then be superimposed on those of congestion as the patient approaches a terminal state. This combination, which is usually observed in acute states before there has been time for the blood volume to increase, is particularly ominous when it occurs in chronic states, despite the increase in blood volume.

Failure of the left side of the heart, with consequent congestion of the lungs, leads to additional changes in the dynamics of the circulation. The rise in pressure in the pulmonary veins and capillaries is reflected into the pulmonary artery, and the thin-walled right ventricle, being subjected to increase in load, empties incompletely, accumulates residual blood, and dilates. Eventually, the sequence of events already described takes place, the ventricular diastolic pressure rising, the emptying of the right atrium being hampered, the atrial pressure rising, the systemic venous pressure increasing, the liver becoming engorged, the loss of blood from the peripheral tissues into the liver and veins causing a further compensatory increase in total circulatory blood volume, and, finally, the pressure in the peripheral veins and capillaries undergoing increase.

*To summarize:* The clinical picture of patients with classic chronic congestive failure appears to be the resultant of two components: (1) The pri-

many alterations occurring in the heart itself, and consisting of decline in contractile power, increase in residual blood, dilatation, and elevation of ventricular diastolic pressure, with consequent alterations in venous pressure and blood distribution. (2) The secondary alterations occurring in the pulmonary and systemic circuits and consisting of congestion and edema with increase in blood and extracellular fluid volumes. The more prominent clinical manifestations, such as dyspnea and edema, are intimately related to these important but secondary alterations.

### HEART FAILURE DUE TO PRIMARY MECHANICAL INTERFERENCE WITH VENTRICULAR FILLING

**1. Disorders of the Pericardium.** Either marked thickening of the membrane or the accumulation of fluid between its layers may cause hindrance to filling. Under such circumstances the contractile power need not be impaired, the systolic emptying may proceed normally, and the ventricular pressure need not be elevated at the onset of diastole. However, the entrance of a relatively small amount of blood will lead to elevation of ventricular diastolic pressure, because the normal distensibility of the ventricles is limited by the fibrous tissue or the intrapericardial fluid. (The characteristic physical signs of cardiac tamponade are discussed in Chapter 236.)

**2. Stenosis of the Atrioventricular Valves.** Such a lesion tends to impede the entrance of blood into the ventricle and constitutes an exception to the otherwise valid rule that heart failure is associated with a rise in ventricular diastolic pressure. However, the atrial pressure tends to rise, as in all types of heart failure, when not complicated by coexisting peripheral failure.

The recognition of these mechanical causes of heart failure is of practical importance because the defect is not in the myocardium, and drugs such as digitalis, which act on the myocardium, cannot be expected to have a favorable effect on the mechanical endocardial or pericardial lesion.

*To summarize:* The fundamental hemodynamic defect in all instances of heart failure is elevation of inflow load in relation to systolic discharge or, expressed otherwise, decline in systolic discharge in relation to inflow load. This defect may occur at any level of cardiac output, which tends to be

high when the primary disorder is increase in inflow load, and low when the primary disorder is defective systolic discharge. Certain disorders cause mechanical limitation of inflow into the ventricles, and hence of output from them. As a rule the ventricular diastolic pressure is elevated, but heart failure caused by stenosis of the atrioventricular valves is exceptional in this respect. However, here, as in other types of heart failure, the atrial pressure is elevated, unless peripheral failure is also present.

Most types of heart failure are due either to myocardial disease or to increased peripheral resistance, and hence are accompanied by primary decline in systolic emptying, with secondary rise in ventricular diastolic pressure. However, the clinical picture depends on the duration of the disorder. When myocardial failure develops rapidly there is no time for secondary increase in blood volume to occur, and the manifestations of decreased cardiac output are outspoken. When myocardial failure develops gradually, secondary increase in blood volume occurs and the manifestations of congestion tend to dominate the clinical picture.

### RELATION OF VARIOUS FUNCTIONS TO CIRCULATORY FAILURE

No necessary relation exists between *heart rate* and circulatory failure, but as a rule there is a moderate to marked sinus tachycardia in persons with peripheral failure. Cardiac failure may be accompanied by various ectopic rhythms, producing either extreme tachycardia or outspoken bradycardia, but is more commonly associated with sinus tachycardia of moderate degree. After prolonged bed rest, resumption of activity may be associated with postural tachycardia, and this may tend to cause heart failure to recur.

The characteristic behavior of blood pressure in patients with acute circulatory failure (whether peripheral or cardiac) has been mentioned, the decline in pulse pressure occurring first, and that in diastolic pressure occurring last. When heart failure develops slowly, slight to moderate rise in diastolic pressure is the rule, the increase in systolic pressure tending to be of somewhat lesser degree.

The blood volume is always affected in patients with circulatory failure, and the alterations may

be either primary (i.e., causes) or secondary (i.e., effects). Furthermore, the changes may be either qualitative (i.e., distributional), or quantitative (i.e., changes in the total circulating blood volume). In the hematogenic type of peripheral circulatory failure there is an absolute decline in blood volume. In the neurogenic and vasogenic types there is a relative decline—i.e., a distributional change with enlargement of the peripheral vascular bed, so that more of the blood is pooled there, and less than normal is in the heart and great vessels.

**Chronic congestive heart failure** is usually associated with an absolute increase in circulating blood volume. Under exceptional circumstances the increase in blood volume may be primary and may be the immediate cause of congestive failure. As a rule the increase in blood volume is secondary, and tends to maintain venous pressures at a high level, and thus to keep up inflow and output toward the normal level, in spite of the resistance to ventricular filling imposed by the increased volume of residual blood in the dilated ventricle. Such a compensatory effect of increased blood volume is only applicable when the heart failure is not too advanced, and when the heart is on the ascending limb of the Starling curve (fig. 25).

**When the heart failure is more severe** and the heart is on the descending limb of the curve, the increase in blood volume will not only augment congestion, but will tend to reduce cardiac output and hence to aggravate the clinical manifestations.

**The mechanism whereby increase in blood volume** occurs in patients with congestive failure is still obscure, and especially the mechanisms responsible for the increase in total amount of plasma protein and red corpuscles. The increase in water and electrolytes is clearly the result of retention of these substances by the kidney. It is generally believed that retention of water is ordinarily the result of retention of sodium. However, the capacity of the patient with heart failure to excrete ingested water is also impaired, possibly as the result of excessive activity of the posterior pituitary.

**When heart failure develops acutely**, increase in total blood volume does not take place in the limited time available, and under such conditions a distributional shift of blood from the periphery to the heart and great veins occurs. This shift apparently is not entirely passive, consequent to

increased pressure in the chambers of the heart, but appears also to be dependent on active constriction of capillaries and venules. There is some evidence, not yet conclusive, that loss of blood from the brain may bring into play mechanisms which lead to increase in total blood volume.

**To summarize:** Peripheral circulatory failure is accompanied by decrease in the volume of blood in the central part of the circulation (i.e., in the heart and great veins). This may be the result either of decrease in total blood volume or of increased size of the peripheral vascular bed. Heart failure, on the other hand, is associated with increased volume of blood in the heart and great veins. This may be related to distributional shift of blood to the heart and great veins from the periphery as the result of increased atrial pressure and increased venocapillary tone, or to increase of total blood volume.

The significance of venous pressure in relation to diastolic inflow has been discussed, and it has been pointed out that, while in the heart-lung preparation the two functions tend to parallel each other, there is no such necessary parallelism in the intact animal because of the other variables.

In peripheral circulatory failure there is a general tendency toward decline in venous pressure, but since the blood volume, and hence the size of the venous stream bed, may be reduced, it is possible to have peripheral failure with marked reduction in output, despite normal levels of venous pressure.

In heart failure the inflow load (and ordinarily the venous pressure) is elevated in relation to cardiac output. In the majority of instances of heart failure, absolute elevation of venous pressure above the normal range occurs. However, the dyspneic state tends to reduce venous pressure, while the distention of the veins leads to enlargement of the stream bed and to increase in blood flow for a given level of venoatrial pressure difference. It is, therefore, possible to have normal level of venous pressure, despite elevation of inflow load in relation to output.

The absolute level of venous pressure in a person with congestive heart failure is dependent upon the balance between mechanisms such as labored breathing, which tends to reduce it, and the several mechanisms which tend to elevate it. Of the latter, hindrance to inflow as the result of

elevated ventricular diastolic pressure (due to the accumulation of residual blood in the ventricle) is probably always the initial factor. Such hindrance will tend to arrest the circulation unless other factors compensate for it. The reduction in cardiac filling will produce accumulation of blood in the great veins. As this occurs the cross-sectional diameter of these veins increases, and the pressure in them rises. The result tends to be a reestablishment of inflow with a diminished pressure difference between veins and atrium which is partially offset by an increase in the size of the central venous stream bed.

If, in the course of these circulatory adjustments, the total blood volume remains constant, the passive shift of blood to the central venous reservoir (brought about by the rise in ventricular diastolic pressure) will necessarily result in a loss of blood from the peripheral venocapillary bed. Whether, in addition, there is an active constriction of this peripheral bed is a matter of difference of opinion. There is strong evidence that this can occur, and that it probably does occur when heart failure develops rapidly or reaches a terminal state, and when there is decline in the size of the peripheral veins. The evidence against venoconstriction in the earlier stages of slowly developing heart failure is as follows: (1) The difference in pressure between the peripheral veins and the atrium is lessened, not increased, in heart failure. (2) Active constriction of the large veins would lead to only a momentary increase in venous filling; the more persistent effect would be a decline as the result of decrease in the size of the venous stream bed. It is difficult to see why a potentially harmful mechanism would occur. (3) In most patients with cardiac failure all visible veins are distended rather than contracted. Pending further evidence, it may be tentatively concluded that active venocapillary constriction is probably a common event in patients with rapidly developing heart failure, and in those with extremely advanced heart failure, but that it is probably not a factor of great significance in the majority of patients with this disorder.

When the heart failure endures for several days or longer, compensatory increase in blood volume occurs, and this leads to further elevation of venous pressure. The rise in tissue pressure consequent to edema tends to prevent escape of fluid from the capillaries, and hence to maintain a high

level of venous pressure. Despite the fact that the rise in ventricular diastolic pressure appears to be the initial factor in all instances of myocardial failure, it is probable that in patients with chronic heart failure the increase in blood volume (and extracellular fluid volume) represents the largest quantitative factor in causing the generalized elevation in venous pressure. This predominant quantitative role of the increase in blood volume is supported by the finding that the venous pressure of patients with congestive heart failure is elevated after death.

The position assumed by the orthopneic patient is a factor of great importance in causing increase in venous pressure in local areas such as the feet and ankles. This is shown clearly by the clinical observation that persons with congestive failure who are free of orthopnea (i.e., certain patients with constrictive pericarditis or with tricuspid stenosis) usually have less edema, despite higher levels of general venous pressure, than do orthopneic persons with the common types of heart failure.

In considering venous pressure in relation to heart failure, it is necessary to distinguish sharply between failure of the two sides of the heart. Failure of the right side of the heart is associated with elevation of systemic venous pressure (either absolute or relative to cardiac output). It has been shown by catheter studies that failure of the left side of the heart is associated with elevation of pulmonary arterial pressure, and very recent observations indicate that such patients display elevation of left ventricular diastolic pressure. Obviously, failure of the left side of the heart can occur in the presence of normal, or even low, values for systemic venous pressure.

When the patient with cardiac failure undertakes exercise, venous pressure rises because the heart is unable to increase its output readily, in response to the augmented rate of venous return.

It has been shown that the difference between peripheral and central venous pressure is reduced in patients with congestive failure. This decline in pressure gradient is apparently related not only to the rise in ventricular diastolic pressure, but also to the increase in the size of the central venous stream bed. Such increase may be due either entirely to a shift of blood from the periphery, as happens when heart failure develops rapidly; or also to the additional factor of an increase in total blood volume, as happens when

heart failure develops slowly. Since the difference between the pressure in the peripheral veins and that in the central venous reservoir is diminished, the finding of peripheral venous pressure values within the upper normal range does not indicate that the ventricular diastolic pressure is not elevated.

*To summarize:* The available evidence is interpreted as indicating that there are several possible causes of increase in the resting level of central venous pressure in persons with myocardial failure: (1) Elevated ventricular diastolic pressure, which appears to be operative (in either the pulmonary or the systemic veins) in all cases. (2) Increase in total volume of the blood and extracellular fluid, which seems to be the most important quantitative factor in instances of slowly developing heart failure. (3) Constriction of the venocapillary bed, which appears to be important in instances of rapidly developing failure, and may be significant when heart failure develops slowly.

The upright position, which is the dominant cause of elevated venous pressure in the dependent parts, tends to reduce rather than increase the pressure in the central venous reservoir.

The time required for blood to pass from one part of the vascular bed to another is known as the "circulation time", which is obviously inversely proportional to the speed of movement of blood. Velocity of blood flow tends to vary directly with volume flow, and inversely with the size of the stream bed (fig. 24). Hence, if the circulation time be measured through the lungs, it will diminish with increase in cardiac output, provided the size of the intrathoracic vascular bed (i.e., the volume of blood in the heart and lungs) remains constant, and will increase if the size of the intrathoracic vascular bed increases, provided cardiac output remains constant.

Peripheral circulatory failure may theoretically be accompanied by no alteration, or a change in either direction in pulmonary circulation time, depending on whether the decrease in volume of blood in the chest or the decrease in cardiac output predominates. In heart failure with pulmonary congestion, on the other hand, the circulation time is prolonged because both factors (the increased size of the vascular bed in the thorax, which is always present, and the decline in cardiac output, which is usually present) tend to

delay the speed of movement of a given unit of blood through the lungs. Such considerations make it clear that since the size of the stream bed always changes when heart failure sets in, the speed of blood flow cannot be utilized as an index to the volume of blood flow—i.e., the cardiac output.

Studies of the cardiac output and cardiac size during exercise, as well as angiocardiographic studies, have indicated that the normal human ventricle does not empty completely during systole. It is, therefore, necessary that a sharp distinction be drawn between the *cardiac output* per unit of time and the completeness of *systolic emptying* per beat, for these functions may vary in opposite directions. Thus, during peripheral circulatory failure, the systolic emptying may be increased despite marked reduction in cardiac output. Heart failure resulting from disorders of the pericardium or from stenosis of the atrioventricular valves may, likewise, be associated with reduced cardiac output, despite an increased degree of systolic emptying. Myocardial failure due to increased peripheral resistance or to primary disorders of the myocardium is associated with diminution of cardiac output and of systolic emptying. On the other hand, myocardial failure due to primary increase in inflow load may be accompanied by increase in cardiac output, despite reduction of systolic emptying. Thus the hallmark of myocardial failure is not decline in cardiac output, but rather reduction of systolic emptying with consequent ventricular dilatation and increase in ventricular diastolic pressure.

Decline in cardiac output relative to the metabolic needs of the body is present in all instances of low-output failure, and in most instances of high-output failure (thyrotoxicosis, anemia, beriberi). However, in the case of heart failure due to primary hypervolemia, failure may occur despite a normal or high level of cardiac output relative to metabolic needs.

It has been pointed out that inflow load is elevated in practically all instances of heart failure, the only exceptions being heart failure accompanied by coexistent peripheral failure and long-standing heart failure treated by prolonged sodium depletion. In such instances the cardiac output is markedly reduced. In those instances of heart failure associated with normal or slightly elevated levels of cardiac output, the inflow load

is markedly increased. Hence it seems justifiable to generalize and to say that all types of heart failure are characterized by decline in cardiac output relative to inflow load. The available evidence suggests that this is the one constant hemodynamic disturbance present in all types of heart failure. In nearly all instances this discrepancy results from increased ventricular diastolic pressure, but heart failure due to stenosis of the atrioventricular valves constitutes an exception to this general rule.

Although the available evidence does not support the concept that reduction of cardiac output in relation to metabolic needs is a necessary and fundamental mechanism of heart failure, it is clear that such a reduction, which is present in the vast majority of instances of heart failure, is often an important cause of some of the clinical manifestations. The significance of diminished blood supply to the tissues in the production of the shocklike state which exists in many instances of rapidly developing heart failure has already been stressed. In patients with long-standing congestive failure, lassitude and apathy may be observed and are, in all probability, to be ascribed to decline in cardiac output. Many believe that such a decline is responsible for sodium retention by the kidney, with consequent hypervolemia, production of edema, and aggravation of dyspnea. It has also been suggested that reduction in cardiac output is responsible for proteinuria, and for central necrosis of the liver lobules, with the secondary formation of venous lakes and the resultant hepatomegaly. Others believe the venous congestion in the kidney and liver, respectively, is of major importance in the production of proteinuria and hepatomegaly. It has been shown in animals that elevation of venous pressure may cause proteinuria.

#### SECONDARY HOMEOSTATIC MECHANISMS IN RELATION TO CIRCULATORY FAILURE

Among the brilliant advances of the past decade have been the elucidation of the alterations in renal function consequent to circulatory failure, and the development of the concept that many of the more important manifestations of heart failure result from the disturbance of normal homeostatic mechanisms. It has been demonstrated clearly that both peripheral and cardiac failure lead to retention of sodium and of water

by the kidney. Such retention causes increase in the total volume of blood and of extracellular fluid, and hence tends to elevate venous pressure, inflow load, and cardiac output (provided the heart is still on the ascending limb of the Starling curve). At the same time, obscure mechanisms cause increase in the total plasma protein and red corpuscle mass, and thus tend to elevate blood volume. Three questions arise: (1) How are these adjustments effected? (2) What is the relation of these adjustments to edema formation? (3) Are such adjustments beneficial or harmful?

The evidence concerning the mechanism of sodium retention in patients with heart failure has been summarized in Chapter 20. Some hold the view that diminished glomerular filtration is the chief factor, but such diminution is not always present. Furthermore, there is evidence that drastic restriction of sodium intake may lead to decline in glomerular filtration. The relative importance of heart failure per se, and of therapeutic depletion of sodium (by mercurial diuretics and by dietary restriction) in the production of the decline in glomerular filtration which is exhibited by most patients with heart failure, is uncertain at present. It appears likely that increase in tubular reabsorption of sodium is the more important factor in the causation of sodium retention.

There is evidence indicating increased adrenal cortical activity in some patients with heart failure, and this may be an important cause of sodium retention. It has been shown that elevation of venous pressure may cause diminished excretion of sodium in the absence of changes in glomerular filtration. It has likewise been shown recently that alterations in fluid balance in the cranial cavity may exert an effect on sodium excretion, the mechanism of the effect and its quantitative significance being as yet unknown. Thus it has been demonstrated that the decline in sodium excretion which normally occurs in the sitting position can be inhibited by compression of the neck. It has, likewise, been demonstrated that intravenous injection of hypertonic albumin solutions causes decline in sodium excretion, and it is possible, although not proved, that the shift of fluid from the tissues into the blood stream constitutes the stimulus to sodium retention under these circumstances. These observations suggest that alterations in tissue fluid (extracel-

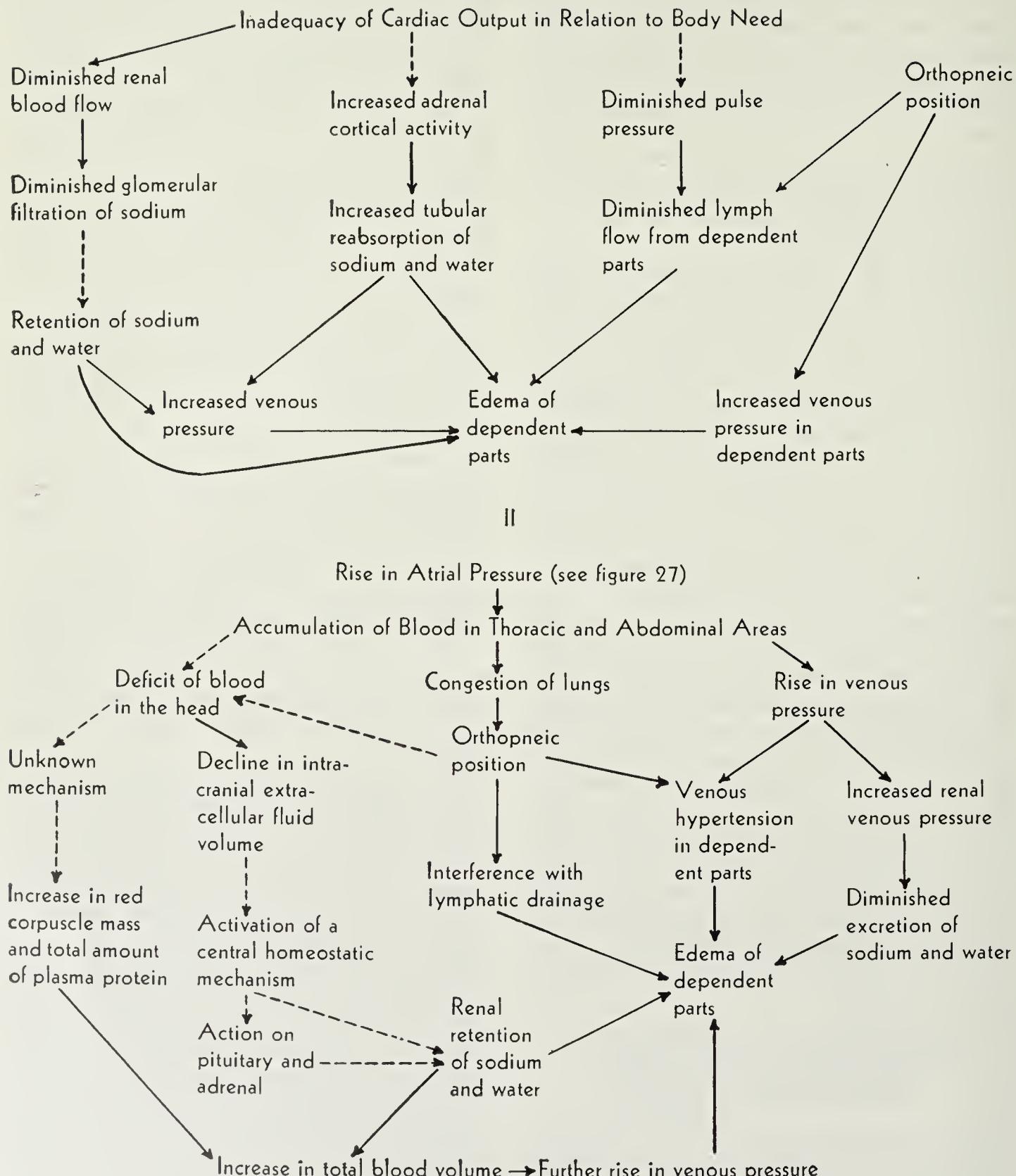


FIG. 26. Diagrams of alternative concepts of edema formation in patients with congestive heart failure. The solid arrows indicate that the mechanism illustrated rests on convincing evidence. The broken arrows indicate that the evidence is somewhat less conclusive, or that exceptions are numerous. The arrows connecting lymphatic drainage and venous pressure with edema are drawn as solid because the two factors are operating simultaneously (p. 170).

Two concepts of edema formation in patients with heart failure are illustrated. According to one of these, the dominant factor is decline in cardiac output with ensuing sodium retention by the kidney. The other hypothesis holds that the initiating factor is rise in atrial pressure with the consequent alterations in venous pressure and in blood distribution, the renal retention of water and electrolytes being secondary. Both points of view hold that the local

lular or intracellular) within the head may constitute one mechanism controlling sodium excretion. When heart failure sets in, the accumulation of blood in the heart, lungs, and great veins, the orthopneic position, and the formation of edema in dependent parts, will all tend to lead to deficit of blood and tissue fluid in the head, until compensatory increase in the total volume of blood and extracellular fluid volume has occurred.

There is another important factor which often plays a role of major significance in reducing the excretion of sodium. This is depletion of the normal sodium stores in the body as the result of the repeated administration of mercurial diuretics, or of the prolonged use of a diet very low in sodium. In certain patients so treated the administration of sodium chloride results at first in retention of sodium without retention of water, and later in restoration of sodium balance at a relatively high level of intake. This observation indicates that sodium depletion may be an important factor in reducing sodium excretion. To what extent such depletion is responsible for some of the other manifestations such as lassitude, asthenia, decline in glomerular filtration, reduction in cardiac output, etc., which are commonly ascribed to the underlying disease rather than to its management, remains uncertain at present.

Another unsettled question is that of the relative importance of the retention of water, sodium, chloride, and of other electrolytes in the pathogenesis of edema formation. It appears that the widely accepted idea that sodium retention is of paramount significance may need to be revised, but further evidence is needed before final conclusions can be drawn.

*To summarize:* The available evidence is interpreted as indicating that increased tubular reabsorption is a more important factor in causing sodium retention than is reduced glomerular filtration. There is as yet no general agreement on the relative quantitative significance of (1) decline in cardiac output, (2) increased adrenal cor-

tical activity, (3) increase in renal venous pressure, (4) decline in extracellular (or intracellular) fluid volume in the cranial cavity, (5) depletion of sodium stores, and (6) unknown mechanisms in the causation of sodium retention (fig. 26).

**Mechanism of Edema Formation in Patients with Heart Failure.** Aside from those mechanisms already discussed, which favor retention of water and of sodium, and hence tend to increase the extracellular fluid volume, there are a number of other important factors to be considered.

A general rise in venous pressure may tend to cause edema through at least three different mechanisms: (1) predominance of mechanical pressure over oncotic pressure in the capillaries (pressure factor); (2) dilatation of capillaries with increase in filtration surface (volume factor); (3) interference with lymph flow from the major lymph channels into the great veins of the neck (lymphatic factor).

Until recently it has been generally assumed that the pressure factor was of primary importance. However, the demonstration that ligation of the inferior vena cava may be followed by only minimal edema, despite tremendous elevation of venous pressure in the legs, necessitates revision of previous concepts. It appears that the lymphatic factor is more important than previously believed because: (1) Elevation of local lymphatic pressure alone, without elevation of venous pressure (chronic lymphangitis, resection of axillary nodes, filariasis), may produce edema. (2) Elevation of local venous pressure without elevation of pressure in the great veins into which the lymph channels drain (ligation of inferior vena cava) causes only slight edema. (3) General elevation of venous and lymphatic pressure (congestive heart failure) is usually associated with outspoken edema. On the other hand, it is clear that general elevation of lymphatic pressure (obstruction of superior cava) does not cause generalized edema, unless venous pressure is also elevated. Apparently, the vascular system and the lymphatic system function, to a limited

FIG. 26—(Continued)

tissue factors predominate in determining the location of edema, and that the renal factor determines the amount of edema. The two concepts, which are not mutually exclusive, differ in ascribing different quantitative significance to the several factors which may be concerned in sodium retention.

Although many believe the upper mechanism (I) to be the more important, others, including the writer, believe the lower mechanism (II) to be quantitatively more significant. According to this concept the disorder tends to perpetuate itself until sufficient increases in total blood volume and total extracellular fluid volume occur to restore these factors in the cranial cavity. Then the cycle would tend to reverse itself. This obviously would occur more readily in those rare types of heart failure (such as that accompanying tricuspid stenosis) in which orthopnea is absent or minimal.

extent, as collateral channels for the escape of excess extracellular fluid. That the volume factor and/or the tissue pressure are also of importance is shown by observations in which one of the legs of a patient with cardiac failure is enclosed by an elastic bandage. Under such conditions, the bandaged leg tends to swell less than the opposite leg.

Sainsbury's suggestion of two decades ago, that the pulse pressure may be an important factor in determining the rate of lymph flow, has now been amply confirmed. Therefore, reduction of pulse pressure consequent to decline in cardiac output will favor edema formation and, more especially, if the rate of passage of fluid from the blood into the tissues is high as the result of alterations in the ratio between oncotic pressure and capillary pressure. However, the occurrence of marked edema in patients with aortic insufficiency, heart block and other conditions associated with elevation of pulse pressure indicate that this factor is not of dominant importance.

Excess of extracellular fluid may develop in a part as the result of a shift from other parts of the body, or as the result of increase in total extracellular fluid volume. It is only the latter mechanism which is induced by retention of sodium and water by the kidney, and associated with increase in weight. Hence, if one uses the weight of the body as the sole index of edema, one will always find that edema is associated with sodium retention.

That edema may appear in the absence of sodium retention (and even when the sodium balance is temporarily negative), may be shown by plethysmographic studies. If a patient with cardiac failure, who has been rendered edema-free by diuretics, be allowed to sit quietly in a chair for a number of hours, the leg volume will increase, even though no sodium and no water are ingested. This indicates clearly that the local tissue factors may be the primary factor in the formation of cardiac edema. Such local factors probably include not only the alterations in capillary, lymphatic, and tissue pressures in the dependent parts but also the loss of fluid from the cranial cavity. However, the degree to which such a purely distributional change in extracellular fluid can take place is very limited, and only slight edema can accrue in a large localized area, unless there is renal retention of sodium and water. Hence there can be no doubt that the

renal factor is the chief quantitative determinant of edema.

The lack of parallelism between venous pressure and edema has naturally led to doubt as to the significance of venous pressure rise in causing edema. However, the effect of posture is all-important here. A patient who has a normal venous pressure as measured at heart level, and who, because of dyspnea, sits up during the 24-hour period, will actually have a greater average level of venous pressure and lymphatic pressure in his legs than another individual who has a higher venous pressure (as measured at heart level), but who spends a large fraction of the 24 hours in the recumbent position. Hence one cannot expect any parallelism between venous pressure and edema, unless the factor of posture throughout the 24-hour period is taken into consideration.

The upright posture tends to produce decline in the volume of extracellular fluid in the cranial cavity, and hence to reduce sodium excretion which ordinarily declines when the sitting posture is assumed, but which remains high if the venous return from the head is partially occluded by compression of the neck. Furthermore, the sitting posture causes rise in venous pressure in the renal veins, which tends to produce sodium retention, and hence to cause edema.

*To summarize:* The level of venous pressure has complex effects on the mechanics of fluid transfer. Local elevation in the dependent parts will favor more rapid escape of fluid from the blood stream. Elevation of venous pressure in the neck will tend to impair lymph flow. Rise in pressure in the renal vein diminishes sodium excretion. On the other hand, it appears that elevation of venous pressure in the cranial cavity will usually tend to have the reverse effect. The available evidence indicates that venous pressure and other tissue factors are predominant in determining where edema will occur, and that these local factors may be primary in determining whether edema will occur. The evidence indicates clearly that the renal factors are dominant in determining how much edema will accumulate. The question as to whether the local tissue factors or the renal factors are to be regarded as primary in the initiation of edema is unsettled at present.

It has been pointed out that the blood volume is always deficient in relation to the size of the

vascular bed in states of peripheral circulatory failure. Retention of sodium and of water tends to restore the blood volume, and is, therefore, clearly beneficial.

In patients with heart failure the problem is more complex. When heart failure develops rapidly (as in a person with acute pulmonary edema due to myocardial infarction) it is attended by a well-marked decline in cardiac output, and by a shift of blood from the periphery to the thorax. (This shift is in part passive and consequent to the rise in ventricular diastolic pressure, which offers hindrance to filling and results in accumulation of blood in the atria, great veins, and, in many instances, the pulmonary capillaries. In addition, there is evidence that active constriction of the venocapillary bed may occur.) Under such circumstances, retention of sodium and water tends to restore the peripheral blood volume to a normal level, and to produce further increment of central blood volume. The rise in inflow load so induced may tend to elevate cardiac output (provided the heart is on the ascending limb of the Starling curve [fig. 25]), and to raise tissue blood flow. The picture of collapse, with slight manifestations of congestion, is thereby converted to the picture of outspoken congestion with slight or no manifestations of collapse.

However, the effects on the patient with heart failure, of such a retention of sodium and of water, are not entirely beneficial. The increased volume of extracellular fluid is not only intravascular but also extravascular, and hence edema is aggravated. Congestion and edema of the lungs tend to be accentuated. Under such circumstances, the temporary abolition of the renal conservatory mechanism by the administration of diuretic drugs is nearly always beneficial, and may occasionally be life-saving.

It will be apparent, from the foregoing discussion, that while the retention of sodium and water by the kidneys in persons with circulatory failure tends to be beneficial when the periphery is primarily at fault, the same mechanism has a twofold effect when the heart is primarily at fault. Here, the operation of the renal mechanism may tend to overcome the decline in cardiac output, but only at the expense of aggravating the congestive phenomena.

When we turn from the kidney and from the subject of retention of water and electrolytes to

the rest of the body, and to the subjects of rise in the total amount of plasma protein and of erythrocytes, little knowledge is available. At present, all that can be said is that circulatory failure tends, through some unknown mechanisms, to produce increment in all of the blood components. The advantage of such increment in states of peripheral circulatory failure, and the twofold effect in the state of heart failure, have been indicated already.

The writer's conception of the sequence of events in patients with heart failure is summarized in figures 27 and 28.

### HEMODYNAMIC EFFECTS OF THERAPEUTIC PROCEDURES

Clinical experience has furnished much information concerning the indications for and the value of the various therapeutic measures employed in combating heart failure, but knowledge as to how and why these measures are effective remains scanty. Important concepts may be gained from study of the Starling curve (fig. 25, p. 153). In a patient with heart failure of such great severity that the dynamic state of the heart corresponds to the descending limb (right portion) of the curve, a decrease in inflow load (such as may be produced by decline in blood volume consequent to venesection or the use of a diuretic drug) will tend to cause not only decrease in congestion, but also rise in cardiac output. Consequently, both the manifestations of congestion and those of defective blood supply will tend to be benefited. In such a patient transfusion will be expected to cause aggravation of both groups of manifestations.

When, on the other hand, heart failure is less severe and the dynamic state of the heart corresponds to the ascending limb (left portion) of the Starling curve, a different situation exists. Now a decrease in inflow load (venesection, diuretic measures) will reduce congestion, but will tend to reduce cardiac output and aggravate the manifestations of defective blood supply to the tissues. Transfusion and edema formation (with accumulation of excess extracellular fluid both in the blood and in the tissue spaces) will have the reverse effect. These conceptions explain why the administration of a diuretic drug may lead to marked improvement in edema and dyspnea but at the same time cause lassitude and asthenia.

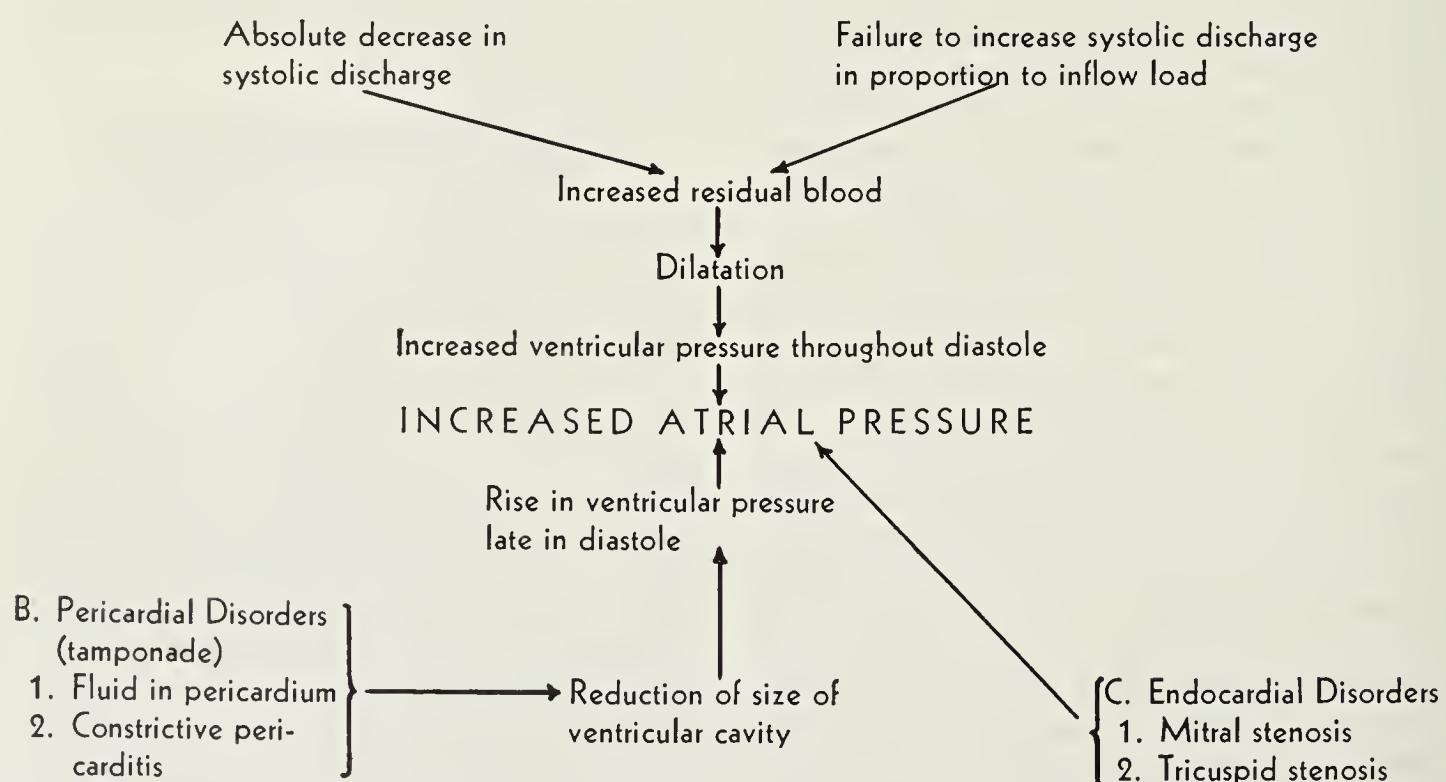
## A. Myocardial Disorders

## I. Primary Decrease in Myocardial Reserve

- 1. Primary myocardial disorders
- 2. Primary mechanical hindrance (e.g., hypertension)

## II. Primary Increase in Inflow Load\*

- 1. Disordered tissue metabolism (e.g., thyrotoxicosis)
- 2. Arteriovenous communications
- 3. Primary hypervolemia (e.g., acute pulmonary edema)



\* These conditions rarely cause heart failure unless the myocardial reserve is also impaired or the peripheral resistance is increased.

FIG. 27. Diagram of different mechanisms whereby heart failure causes elevation of atrial pressure. The primary myocardial disorders (I, 1) include not only the various structural diseases, but also those arrhythmias, such as the ectopic tachycardias, which reduce systolic discharge.

It is possible to produce heart failure in the animal or in man with a previously normal myocardial reserve, by an increased inflow load of sufficient severity and duration. This is seen occasionally in a child or young adult who has been treated with massive amounts of intravenous fluids following extensive burns. As the skin improves and the fluid is reabsorbed, the typical signs of the overactive heart may appear, and these may be followed by severe and even fatal congestive failure. In most instances, however, the increase in inflow load is not sufficient to produce heart failure unless the myocardium is already impaired by preexisting disease (usually of the senile type) or by mechanical strain (most commonly hypertension).

Heart failure due to tamponade differs from that due to myocardial disturbances in that there is no difficulty in emptying, and hence the rise in ventricular diastolic pressure occurs in the latter part of diastole (because of impairment of further filling) rather than at the onset of diastole (because of defective emptying during the previous systole).

Endocardial disorders may affect the heart in various ways, such as by causing an increase in inflow load (aortic insufficiency) or by hindering the process of emptying (aortic stenosis). However, the hemodynamic defect which is peculiar to endocardial disorders is that which occurs with stenosis of the atrioventricular valves, and which leads to a rise of atrial pressure without a preceding increase in ventricular diastolic pressure.

The diagram illustrates the fundamental principle that the cardinal hemodynamic defect of heart failure is reduction of output relative to inflow load, and that this discrepancy ordinarily manifests itself by elevation of atrial pressure.

**I. Primary Mechanisms  
(All heart failure)**

**A. Myocardial, Pericardial and Endocardial Disorders**

Increased atrial pressure  
(see figure 27)

Decreased inflow from veins

Rise in venous pressure

Accumulation of blood in heart and great veins

Deficit of blood in periphery

Inability of ventricle to empty adequately

Increased diastolic inflow and cardiac output

**B. Excessive Inflow Load  
(see figure 27)**

Decreased cardiac output

Clinical picture of collapse

Manifestations of congestion

Obscure mechanisms

Alleviation

Aggravation

Renal retention of Na and H<sub>2</sub>O

Increased quantity of plasma proteins

Increased total red corpuscle mass

**II. Secondary Mechanisms  
(In slowly developing heart failure)**

Rise in cardiac output\*

Further increase in inflow load

Further congestion

Further increase in central venous stream bed

Increased total blood volume

\* Provided the heart can still respond (i.e., is "on" the ascending limb of the Starling curve).

FIG. 28. Primary and secondary hemodynamic mechanisms in heart failure. The diagram attempts to separate sharply those features of heart failure which are regarded as primary and which are considered as occurring in all instances of heart failure, and those which are believed to be secondary and to occur when time is sufficient for certain adjustments to be made. These adjustments are compensatory in one sense, in that they may tend to alleviate decline in cardiac output, but are harmful in that they tend to aggravate congestion.

It should be noted that absolute decline in cardiac output is not present in all instances (B), but that decline in output relative to inflow load does occur in all instances (A and B).

The diagram is constructed on the assumption that the failing heart is still "on" the ascending limb of the Starling curve (fig. 25). This assumption is probably correct in most instances, but is probably incorrect in patients with extremely severe heart failure. If the heart is "on" the descending limb of the Starling curve, the right upper portion of the diagram would need to be modified. Under such circumstances the increasing inflow load would cause fall in cardiac output and aggravation rather than alleviation of the clinical picture of collapse.

The solid and dotted lines represent alternative conceptions of the sequence of events.

The action of digitalis in relation to the Starling curve will be considered in Chapter 238.

The problem often arises in a patient with acute myocardial infarction or with some other disorder producing cardiac failure resembling peripheral failure, as to whether transfusion is indicated. Theoretically, this procedure should be harmful—both as regards congestion and collapse—if the heart is on the descending limb of the Starling curve. If the heart is on the ascending limb, the procedure should benefit collapse but aggravate congestion, and the decision as to whether to transfuse or not would be based on whether or not the clinical picture were dominated by dyspnea or by the shocklike state. Unfortunately, there does not exist at present any simple clinical method of ascertaining the status of a given patient in relation to the Starling curve. Quantitative measurements of cardiac output in relation to venous load in patients with congestive failure are relatively few, and have not yielded consistent results. Measurements of the response of pulse rate and pulse pressure to exercise make it appear highly probable that most patients with chronic congestive failure are on the ascending limb, but proof is lacking. The development of a simple clinical method of determining the functional state of the heart in relation to the Starling curve would constitute a major advance in the evaluation and management of patients with heart failure.

### MIXED TYPES OF CIRCULATORY DISTURBANCES

Under certain circumstances the various general circulatory disturbances may occur in combinations of which the following are the most important:

1. "**High-output failure**" is the term applied to instances of congestive heart failure developing in persons with the syndrome of the overactive heart. This is heart failure due to primary increase in inflow load, rather than to primary decrease in systolic discharge. As has been indicated (p. 159), this type of heart failure may be induced by at least three different mechanisms—i.e., (a) disturbances in tissue oxidation, (b) arteriovenous shunts, (c) primary hypervolemia. In most instances it is accompanied either by myocardial disorders or by increase in peripheral resistance.

2. **The combination of congestion and collapse** occurs under a number of different circumstances. The most common cause, acute heart failure, has been considered in some detail. Two somewhat different mechanisms may be involved: (a) *Symmetric acute heart failure*: Here, the two sides of the heart are affected equally, and the dynamics consist of a shift of blood from the periphery to the central regions. Paroxysmal tachycardia, with signs of collapse but with slight congestion of the lungs and slight venous distention, is an example. (b) *Asymmetric acute heart failure*: Here, one ventricle (usually the left) fails but the other does not. Blood shifts from the periphery to the lungs. In so far as the right side of the heart is concerned, the dynamics are those of peripheral circulatory failure, with reduced venous inflow because of loss of blood from the periphery. However, in so far as the left side of the heart is concerned, the dynamics are those of heart failure. A common example of this situation is acute coronary occlusion with congestion and edema of the lungs, and reduction of peripheral venous pressure. In time, such a state usually changes to that of symmetric heart failure, as the rise in pulmonary pressure and in inflow load (due to secondary increase in blood volume) induces failure of the right ventricle.

Peripheral circulatory failure may eventually lead to heart failure as the result of prolonged decline in arterial pressure with deficient coronary blood flow. Likewise, heart failure may be complicated by peripheral failure when prolonged restriction of sodium or excessive administration of mercurial diuretics leads to reduction of blood volume in relation to size of the peripheral vascular bed, dilated by the previous long-standing congestion. Regardless of which disorder is primary, the coexistence of peripheral failure may lead to a condition in which heart failure exists despite a normal level of atrial pressure. In the absence of coexisting peripheral failure, the available evidence indicates that atrial pressure is always elevated when the heart fails.

When peripheral and cardiac failure coexist, a grave therapeutic dilemma arises. Procedures which tend to improve the one are likely to aggravate the other.

3. **Aortic or Mitral Regurgitation.** Another type of mixed failure is that due to aortic or mitral regurgitation. Here, the left ventricle may

fail because of primary increase in inflow load as the result of the valvular defect. On the other hand, right ventricular failure developing secondarily in such instances is the result of primary decrease in systolic discharge consequent to the increased resistance in the pulmonary vascular bed.

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## Section 5—Indigestion and Jaundice

# 15

## Indigestion, Dysphagia, Nausea, and Vomiting

William H. Resnik

Indigestion  
    Definition  
    Visceral Pain  
    Common Syndromes Expressed as Indigestion  
    Differential Diagnosis  
    Procedure in Investigation of Chronic Indigestion

Dysphagia  
    Dysphagia Due to Mechanical Obstruction in the Esophagus  
    Dysphagia Due to Disturbance in the Neuromuscular Mechanisms of Swallowing  
    Dysphagia Due to Lesions of the Mouth, Pharynx, or Larynx, Causing Pain or Mechanical Hindrance to Passage of Food into the Esophagus  
    Differential Diagnosis  
    Procedure

Nausea and Vomiting  
    General Principles  
    Effects of Vomiting  
    Classification  
    Differential Diagnosis

### INDIGESTION

**Definition.** Indigestion, or dyspepsia, has no sharply defined meaning. Some authors restrict the term to a multitude of symptoms aside from outspoken pain: heartburn and acid regurgitation, nausea and vomiting, gaseous distention and belching, and the various forms of distress such as a feeling of fullness or pressure that cannot be cataloged strictly as pain. Here we shall consider indigestion as constituting any of the above symptoms, including the chronic recurrent types of pain, the severity and character of which fall short of placing them among the acute abdominal emergencies—a distinction not always easy to make.

**Visceral Pain : GENERAL PRINCIPLES.** Depending on the origin, abdominal pain may be either somatic or visceral. *Somatic* pain is the designation given to pain arising in the parietal peritoneum or the dome of the diaphragm, the impulses being conveyed by the intercostal or the phrenic nerves. *Visceral* or splanchnic pain originates in certain of the hollow viscera or closely contiguous structures such as the mesentery, the afferent impulses being carried in sensory nerves that run in the sympathetic system. Both so-

matic and visceral afferent impulses eventually terminate in the posterior root ganglions and from here are relayed through the cord to the higher centers that ultimately give rise to consciousness of pain.

For a variety of reasons, certain important questions pertaining to digestive tract pain continue to remain a subject of controversy. Some of the comments to follow bear on the problem of visceral pain in general, but they are introduced here because they are especially pertinent to the more specific problem of digestive tract pain. One important matter that has aroused debate is the very existence of visceral pain. The fact that abdominal viscera such as the stomach and intestines have been found, during operation on conscious human beings, to be insensitive to stimuli such as burning or cutting has raised doubt as to whether the viscera are ever a direct source of pain. Nevertheless, the preponderance of evidence leaves no doubt that at least certain viscera can be the immediate origin of painful sensations provided adequate stimuli are operative.

This leads to a second disputed question: What are the "adequate" stimuli to the sensory nerves mediating pain in the digestive tube? Clinical and experimental observations have demonstrated that abnormal tension in the walls of the gut may give rise to pain. During the course of the last several decades the principle has evolved, and has gained almost universal acceptance, that tension is the only stimulus to pain in the digestive tract. However, other work on the nature of the stimulus responsible for the pain of peptic ulcer (to be discussed later) throws serious doubt on the validity of the tension theory as the sole explanation for the provocation of pain in the gut. It will suffice here to conclude that tension in the walls of the digestive tract or on the adjacent mesentery may arouse certain types of

pain (e.g., intestinal colic), but that other stimuli, such as acid irritation of a broken mucosa, may also give rise to digestive tract pain.

A third and extremely important problem is the mechanism underlying referred visceral pain. As compared with the superficial, burning, and sharply localized character of pain originating from a superficial structure such as the skin, visceral pain tends to be deep, aching, more or less diffuse, and poorly localized. Moreover, visceral pain is frequently distributed in a segmental pattern. Thus, the pain of gallbladder disease may be felt in the right subscapular area, and that of a duodenal ulcer at or just below the xiphoid or at the corresponding segmental level of the back. This phenomenon—the projection of visceral pain to the skin and more superficial structures of the body, often at a distance from the source of the pain—is spoken of as “referred visceral pain.” Until recently there have been two dominant hypotheses regarding the mechanism mediating referred visceral pain. According to one view, afferent visceral impulses travel to the cord and spread from the gray matter representing the viscera to areas in the same segment of the cord representing somatic structures. From here, impulses are then conveyed to higher centers which interpret the sensations as coming from the skin areas of the corresponding segments of the cord. Thus (it is assumed), pain is distributed in consciousness to superficial areas of the body when in actuality the painful stimuli originate in a viscera whose afferent fibers happen to terminate in the same cord segment. This hypothesis also contends that the impact of the visceral stimuli establishes an irritable focus in the cord which is responsible for the cutaneous tenderness, the involuntary muscle spasm, and the deep muscular tenderness commonly found in the involved somatic area in association with visceral disease. According to a second hypothesis, the splanchnic fibers are incapable of carrying painful sensations, hence referred visceral pain cannot be evoked by stimulation of the splanchnic fibers. Following this concept, referred visceral pain is aroused only when somatic fibers in the parietal peritoneum or mesentery are irritated. When these latter are involved, then only is referred visceral pain possible, the sensation being localized in the superficial areas innervated from the same segments of the cord.

These two hypotheses are founded on the fun-

damental premise that the afferent nervous supply to the viscera, coursing through fibers that run in the sympathetic chain, is basically different, physiologically as well as anatomically, from the afferent nervous mechanism that supplies the somatic tissues. The researches of Kellgren and Lewis have thrown fresh light on the problem of visceral pain. These investigators found that, by irritating deep somatic tissues at various segmental levels, the clinical features of various visceral disorders such as renal colic, gallbladder colic, and angina pectoris could be accurately reproduced. Thus, to cite one example, injection of a small amount of irritating solution (hypertonic saline) into the first lumbar interspinous ligament aroused all of the clinical phenomena characteristic of renal colic. As a result of these and other experiments they concluded that, from the standpoint of physiologic behavior, the sensory innervation of the viscera and of all the deep somatic structures is fundamentally similar. Both sets of sensory nerves constitute a single deep sensory system whose response is identical, whether the deep somatic tissues or the viscera are the source of the pain. Whether these two sets of peripheral nerves actually end around common neurons of the second order in the spinal cord is uncertain, but the qualities of the pain are such as to make such an explanation seem reasonable. The deep, diffuse, and often frankly segmentally distributed pain, as well as the cutaneous hyperalgesia, involuntary muscle spasm and deep muscular tenderness, are phenomena characteristic of stimulation of the deep sensory nervous system, irrespective of whether the afferent splanchnic nerves or the deep somatic sensory nerves are involved. Unlike the skin, which is so accurately represented in the sensorium that localization within a few millimeters is possible, the localization of pain arising in the deep tissues, somatic or visceral, is far less precise, and only in a general way can the sensorium recognize the entire area governed by the cord segment in which the stimulus arises. According to this view, segmental reference is a form of faulty localization, natural and inherent in the deep sensory system, and these investigators reject the assumption of a hypothetic irritable focus in the cord, or the idea that referred visceral pain is a function only of the somatic nerves. The localization of deep pain merely affords information regarding the affected segment of the cord. It is only when we consider

the circumstances that bring on or relieve the pain, and what Lewis describes as the time-intensity curve of the pain (whether it is throbbing or continuous or colicky), that we can begin to draw more definite conclusions regarding its nature.

**LOCALIZATION AND OTHER CHARACTERISTICS.** Regardless of which view is ultimately accepted as the correct explanation for the mechanism of referred visceral pain, it is implicit in all that the localization of visceral pain is dependent on the segments of the cord subserving the affected viscera. Clinical experience, supported by experimental evidence, has emphasized the importance of careful observation of the location of abdominal pain in determining at what level of the gut the pain originates. Distention of balloons accurately placed at different levels throughout the gut has yielded valuable data of clinical importance, correlating the site of the affected segment of the digestive tract with the corresponding localization of pain.

Table 11

## DISTRIBUTION OF PAIN ON THE BASIS OF CLINICAL AND EXPERIMENTAL DATA

Origin of Pain	Location of Referred Pain
Esophagus.....	Behind sternum, predominantly at level of xiphoid or suprasternal notch
Fundus of stomach.....	Left lower anterior region of chest and left side of epigastrium
Stomach and first part of duodenum.....	High epigastrium
Gallbladder and extrahepatic biliary ducts	High epigastrium, right side of back
Pancreas.....	High epigastrium, left side of back
Small intestine.....	Region of umbilicus
Colon.....	Below umbilicus
Rectosigmoid.....	Low in abdomen, just above symphysis

In general, the abdominal pain is referred to the anterior midline. Midline localization is less marked in the case of pain originating in the colon, and there is a definite tendency for disturbances in the cecum, hepatic and splenic flexures, and sigmoid to cause pain in the vicinity of the respective areas of the colon. At times the pain may be felt in the back as well as in the anterior abdominal wall, and occasionally it may be felt in the back alone.

The character of the pain, whether produced experimentally or occurring spontaneously, is decidedly less consistent than is its localization, and hence has more limited clinical value. Indeed, there are very few types of abdominal or digestive tract pain that are so definitely characteristic as to have clinical significance. One exception is *heartburn* (a sensation of warmth behind the lower sternum). This has been shown to arise predominantly, if not exclusively, from irritation of the lower esophagus. Hence the occurrence of heartburn should immediately arouse suspicion of the lower esophagus as the primary source of this symptom, or as the site of reflex disturbances secondary to other lesions or functional disorders in the gastrointestinal tract. *Colicky pains* (intermittent cramping sensations) are indicative of intense and recurrent spasm in a hollow viscus, usually due to peristalsis acting on gaseous rather than fluid content, but occasionally due to obstruction. *Severe localized pain*, associated with involuntary muscular rigidity, cutaneous hyperesthesia, localized tenderness, and rebound tenderness, points to irritation of the parietal peritoneum. All these phenomena, with the important exception that rebound tenderness is absent, may be encountered without peritoneal involvement, in conjunction with disturbances of certain abdominal viscera—for example, gallstone colic. The experimental work of Lewis and Kellgren demonstrates that under these circumstances the findings are reflex manifestations. These three types of pain have distinctive quality in that the character of the sensation per se has diagnostic import; other types of abdominal pain are more vague and are recognized by precipitating and alleviating factors rather than by the quality of the discomfort itself.

The severity of abdominal pain varies so widely from individual to individual that too much weight cannot be placed on this characteristic alone. In general, the more severe the pain, particularly if it arouses a patient from sleep and requires the use of a hypodermic of morphine, the more likely is its cause to be some organic disease, but exceptions are common. A transitory disturbance of little fundamental importance may occasion an apparently exruciating pain; a lesion of serious potential or actual gravity may cause little or no pain.

Careful analysis of the circumstances under which abdominal pain is provoked or relieved

contributes information of the highest importance in the analysis of the origin of the pain. A clear-cut relationship to effort will indicate the heart as the responsible organ in some cases of upper abdominal pain attributed to indigestion. (Actually, a careful history usually will reveal that the "abdominal pain" of angina pectoris is usually not abdominal but behind the lower sternum, the patient tending to describe it as abdominal because he thinks it is due to indigestion, and therefore assumes that it should be in the abdomen.) Relief by food or alkali will suggest the presence of a peptic ulcer. Induction of pain on assuming the recumbent position or on leaning forward to tie a shoelace may be the clue to the existence of a diaphragmatic hernia. The colon will be suspected when abdominal pains are influenced by the passage of gas or by defecation. These examples are cited to illustrate the principle that the circumstances that attend the appearance and relief of abdominal discomfort have a significance second to none in assessing the meaning of abdominal pain. Obviously, the presence of other associated manifestations that have localizing value is also important: localized rigidity and tenderness of the abdominal musculature, hematemesis, melena, and jaundice. An elevated sedimentation rate should serve as a warning signal in any condition presumed to be due to a functional disorder. The appraisal of abdominal pain or indigestion requires a careful consideration of all the features that have been mentioned: the location of the discomfort, its character and intensity, the circumstances provoking and relieving it, the associated findings, as well as the data pertaining to the age, sex, and environmental factors surrounding the individual.

**Common Syndromes Expressed as Indigestion.** The digestive tract responds to abnormal stimuli by alterations in secretory and motor activity. It is the abnormal motor activity which is, in large part, the cause of the various forms of indigestion, and the more important syndromes due to this type of disordered function, expressed as indigestion, will be outlined.

**ANOREXIA.** Anorexia is a symptom, not a syndrome, but is discussed here because of its importance. There seems to be no distinct physiologic basis for loss of appetite. In some (probably most) cases in which correlation of gastric function with anorexia has been made, inhibition of gastric activity has been found. However, it has

been shown that under certain conditions the converse may be true: loss of appetite may occur when gastric functions (secretory and motor activity) are enhanced. These contradictory findings emphasize the more complex nature of appetite as compared with hunger, and indicate the large role that various psychic influences play in determining the presence or absence of appetite.

Clinically, anorexia occurs in so many conditions of ill health, both psychogenic and organic, that its diagnostic significance has little value in the light of other more positive manifestations that signify the nature of the underlying disorder. In some cases loss of appetite may be the only symptom in a person in whom the history, physical examination, and routine laboratory examinations reveal no adequate cause. Under these circumstances, it is important to remember that anorexia may be the sole clue to the presence of a malignant growth in the digestive tract, particularly in the stomach or colon. Increased weight is attached to the symptom if it occurs in a middle-aged or older individual whose previous appetite has been good.

**EARLY POSTPRANDIAL INDIGESTION.** When food is ingested by a normal individual, a prompt diminution in the tone and peristaltic activity of the gastric musculature ensues. The subsequent motor activity incidental to the process of digestion goes on below the level of consciousness. When the normal motor responses are disturbed and gastric tone is enhanced rather than relaxed by the entrance of food into the stomach, the resultant effects of the abnormal tension in the gastric wall are felt as indigestion coming on immediately or shortly after the taking of food. The symptoms appear in different forms and combinations: a feeling of pressure or fullness or actual pain, nausea and vomiting, belching of gas, heartburn (presumably due to reflex alterations in the lower esophageal wall or irritation of the esophagus by regurgitation of gastric contents), etc. These symptoms persist for a variable period of time, sometimes curtailed by vomiting, spontaneous or induced, and the subject then experiences relative or complete relief until the next meal is taken. Such early postprandial discomfort may be due to a wide variety of causes and hence has little diagnostic significance. Its presence is simply an indication for careful search for all of the conditions (intraabdominal, extraab-

dominal, and psychogenic) which may cause indigestion.

**LATE POSTPRANDIAL INDIGESTION.** In other individuals, indigestion is experienced only after a period of time has elapsed after the ingestion of food—usually one or more hours. As in early postprandial indigestion, the symptoms may consist of heartburn, nausea, epigastric fullness, or fluctuating pains in various combinations. The location of these symptoms indicates their origin to be in the esophagus or stomach or duodenum, and they are probably due to disturbances in the muscular tension of these organs. At times the discomfort is in the distribution of colon pain, either below the umbilicus or in the region of the flexures, presumably due to an overactive gastrocolic reflex. The classic example of late postprandial indigestion is encountered in uncomplicated peptic ulcer, typically described as a deep, gnawing, *steady* pain of long duration, felt high in the epigastrium. Ulcer pain is not of brief duration (few moments), nor does it fluctuate in intensity from moment to moment. Several hypotheses have been advanced as explanations of the mechanism of ulcer pain. The two most widely held attribute the pain to (1) increased tension in the muscular walls of the stomach or duodenal cap and (2) irritation of the ulcer by the acid of the gastric juice. The tension theory is supported by the fact that exertion of pressure on the walls of the stomach or duodenum, either by distention of properly placed balloons, or by forceful application of a glass rod against the interior of the stomach, can elicit the gnawing, steady pain characteristic of ulcer. These observations demonstrate that tension can be an adequate stimulus to the pain receptors in these organs, but the proof that it is the actual stimulus to ulcer pain is quite inconclusive. Although the evidence is conflicting, the most carefully controlled and the most convincing work shows that not only is tension not increased during the period of ulcer pain, but it is usually diminished. On the other hand, there are other observations that are so impressive in support of the acid irritation theory that it is difficult to escape the conclusion that the pain of peptic ulcer in the active stage is ordinarily due to stimulation of the sensory nerve endings in the ulcer by suitable concentrations of acid. This conclusion is of more than academic interest, for it leads to two further inferences of practical importance: (1) deep,

steady pain occurring some time after eating (an hour or more) and relieved by food, alkali, or vomiting (in each instance diminishing the concentration of acid) implies the irritating effect of acid on a defective membrane of the stomach or duodenum; (2) such pain occurring during the course of ulcer treatment implies inadequate neutralization of the acid. Opponents of the acid irritation theory cite what appears to be a formidable array of clinical observations that seem to refute the conception that ulcer pain is due to the action of acid on an ulcerated surface of the stomach or duodenum, the most important being that typical ulcer pain may be seen in patients who have no demonstrable ulcer or, in rare instances, who are reported to have no free acid in the gastric juice. Whether in patients with acid in the gastric juice but without demonstrable ulcer, superficial ulceration exists even though not visualized by x-ray, or whether in the rare case of supposed ulcer pain but without free acid, a true ulcer pain has actually been present, or whether some other mechanism apart from acid irritation of a mucosal defect is responsible for ulcer-like pain in some instances, cannot now be answered with certainty. Despite these gaps in our knowledge, acid irritation of an ulcerated surface seems to be the most satisfactory working basis as the explanation of ulcer pain.

The types of indigestion do not always divide themselves neatly into these patterns of early and late postprandial discomfort. In some instances both the early and the late forms may be seen in the same subject, as well as indeterminate types that are so irregular that they defy classification. Late postprandial indigestion of the kind described above as being characteristic of ulcer pain immediately suggests benign peptic ulcer, but essentially the same pain may be witnessed in other disorders such as carcinoma of the stomach with hyperacidity, ulcerative gastritis, or duodenitis. Late postprandial indigestion that does not conform to the characteristics of ulcer pain may be due to a wide variety of other primary or reflex disturbances of the stomach.

**PYLORIC OBSTRUCTION.** Obstruction of the pylorus due either to organic stenosis or to spasm and edema usually is associated with the early appearance of indigestion, sometimes continuous, and hours later culminating in colicky epigastric pains and the retention type of vomiting.

**INTESTINAL OBSTRUCTION AND PARALYTIC ILEUS.** Acute obstruction of the bowel, if complete, is an emergency of such magnitude that it cannot be considered to fall into the province of the disorders now under discussion. However, incomplete obstruction may give rise to periodic bouts of cramplike pain, nausea, and vomiting, sometimes accompanied by distention. These symptoms, when mild, may be considered "indigestion" by the patient. The characteristic picture is less likely to be evidenced in partially obstructive lesions of the large bowel, particularly in the cecum, where extensive lesions may be present without giving rise to any obstructive phenomena.

Ileus, associated with distention, nausea, and vomiting, is frequently present in acute pancreatic edema. It is not unusual in active stages of cirrhosis and hepatitis, and is seen occasionally in cardiac failure or during recovery from shock, or with peritoneal irritation from tuberculous or carcinomatous peritoneal implants, as well as in suppurative peritonitis and mesenteric thrombosis. Air swallowing or impaired circulation of blood in the gut increases the gas content of the small bowel and causes griping pains, or "gas pains."

**Differential Diagnosis.** A detailed outline of all the causes of recurrent indigestion is obviously impossible. However, certain principles that may be used as a guide in the analysis of chronic indigestion may be discussed. In every case the following questions must be answered: (1) Are the symptoms due to organic disease outside the digestive tract, or to organic disease within the digestive tract (including the gallbladder and extrahepatic biliary passages), or to a functional disturbance? (2) If organic disease of the digestive tract is present, is the lesion malignant or benign? (3) If the disorder is functional, is its origin psychogenic or nonpsychogenic (allergy, hypoglycemia, drugs, reflex effects)? The classification of indigestion on the basis of the fundamental lesion being primarily in the alimentary canal, or outside it, must in some instances be an arbitrary one. For example, indigestion may be a prominent feature of pernicious anemia, a condition which is associated with structural alterations in the stomach that may be the actual root of the disease. Nevertheless, tradition has placed this disorder among the diseases of the hemopoietic system.

**INDIGESTION DUE TO ORGANIC DISEASE OUTSIDE THE DIGESTIVE TRACT.** A complete catalog of all the conditions outside the digestive tract capable of causing indigestion would serve to do little more than call attention to the fact that diseases of practically all systems of the body may at times be accompanied by indigestion in one form or another. The presenting complaint of the patient with pernicious anemia, pulmonary tuberculosis, myocardial failure, chronic infection of the urinary tract, or disease of the pelvic organs, may be dyspepsia. Migraine, epilepsy, or other disturbances of the central nervous system may manifest themselves in chronic abdominal complaints. The digestive symptoms vary in detail and severity, and have no characteristics that betray the fact that they are secondary to some more remote malady. Recognition of these multitudinous causes of indigestion can come only from meticulous regard for all the details of a complete history and physical examination and the laboratory tests necessary for accurate diagnosis.

**PEPTIC ULCER.** The characteristic qualities of the pain of uncomplicated ulcer of the stomach or duodenum are its rhythmicity and periodicity. The rhythmicity refers to the pain-food-ease sequence, the classic prototype of the late postprandial form of indigestion. The periodicity expresses the tendency for the indigestion to appear for weeks at a time and later to disappear for months, over the course of a number of years. Ulcer is far more common in the duodenum than in the stomach, and the incidence in males is higher than in females. Ulcer may develop at any decade, but gastric ulcer is rare before the age of 40. The usual location of the pain is in the high or midepigastrium; vomiting occurs infrequently in uncomplicated ulcer; pain before breakfast is practically never seen. As complications develop, the clinical picture tends to become distorted and to lose its usually sharply drawn lines. In cases of penetration with extension into the surrounding tissue, the characteristic pain-food-ease pattern tends to be less clearly delineated, the pain becomes more continuous, and radiates more widely as the nerves of the involved tissues become affected. Obstruction at the pylorus is also heralded by alteration of the classic ulcer syndrome: earlier onset of pain, often with the loss of relief by food and alkali, and the appearance of vomiting of the retention type.

**CARCINOMA OF THE STOMACH.** The traditional history of anemia, loss of weight, strength, and appetite, and discomfort of variable intensity and form after eating, usually represents an advanced carcinoma of the stomach. It is now appreciated that the early stage of carcinoma of the stomach presents a picture of considerable diversity, dependent on the location and extent of the lesion. If the growth exists at the cardia or pylorus, early obstructive phenomena may be witnessed. If the lesion is small and ulcerated and if the gastric juice contains free hydrochloric acid, the clinical picture of a benign peptic ulcer may be reproduced so perfectly in its symptoms, roentgenologic appearance, and even in its temporary response to treatment, that clinical differentiation may be practically impossible. In some cases the digestive symptoms, though present, may be so mild and vague as to be hardly suggestive of any serious disorder. Finally, in a considerable number of instances, especially those with achylia, no gastric symptoms occur until anemia, wasting, or other changes are fully displayed. In short, not only is the indigestion of early carcinoma of the stomach lacking in any definitive features that are indicative of the causative lesion, but the entire clinical picture may be equally uninformative. The inevitable consequence of these observations is that any indigestion in the upper abdomen not otherwise clearly accounted for, particularly when it occurs in a male over the age of 40, should be suspected of having its origin in a malignant lesion of the stomach, and should be carefully studied by every available method with this possibility in mind. Lesions on the greater curvature are practically invariably malignant, and those in the prepyloric region close to the pylorus are malignant in over 90 per cent of the cases; any ulcer of the stomach that fails with adequate treatment to diminish considerably in size within three weeks, or to heal completely within six weeks, as determined by serial x-ray studies, by stool examinations for occult blood, and by gastroscopic examination, should be considered a possibly malignant lesion.

**CHRONIC GALLBLADDER DISEASE.** The symptoms of chronic gallbladder disease are of two kinds, indigestion and colic. The indigestion may occur early or late after a meal, and is lacking in any distinctive qualities that permit a diagnosis of the basic disorder. Intolerance to fats is some-

times described as a characteristic feature. Carefully taken histories disclose that, when the patient does have an intolerance to certain foods, nonfatty foods are frequently incriminated as well as the fatty ones, that some fats are accepted when others are not, and that the particular fats that bring on symptoms vary with different individuals. Fat intolerance is, therefore, not a symptom that is an expression of an inability to handle fats alone, but is rather one feature of a much broader food intolerance that applies to nonfatty foods as well, and that differs in its details from patient to patient. It is more accurate, then, to speak of food intolerance rather than fat intolerance as being a common symptom in chronic gallbladder disease. However, this kind of food intolerance is not peculiar to chronic gallbladder disease alone. Exactly the same intolerance to foods, fatty as well as nonfatty, is encountered in patients who suffer from functional disorders or from a variety of other organic ailments in the absence of any demonstrable disease of the biliary tract. In other words, *neither the indigestion nor the so-called fat intolerance that is sometimes ascribed to gallbladder disease is distinctive*. It may be added that since there is no evidence that in the absence of obstructive jaundice all fats are poorly digested and tolerated, there is no justification for the common practice of severely restricting the use of all fats in the diets of patients with chronic gallbladder disease. As in patients suffering from allergic disorders, dietary restrictions should be made according to the individual problems of the patient. There is no rational basis for any diet that is applicable to all patients with chronic gallbladder disease.

Apart from the indigestion, the patient with chronic gallbladder disease is often subject to more or less severe attacks of biliary colic. It is these acute attacks of pain, localized high in the epigastrium or in the right (rarely in the left) hypochondrium, radiating to the right subscapular or to the interscapular regions, or sometimes to the tip of the right shoulder, which are really suggestive of gallbladder disease; when they are associated with jaundice, the diagnosis becomes clear. The frequency of this condition renders suspect every woman over the age of 25, particularly if she has borne children, and all individuals over the age of 40, complaining of indigestion. Fortunately, the diagnosis is capable of confirmation in a high percentage of cases by cholecystog-

raphy, particularly since the introduction of iodoalphionic acid ("Priodax") as the gallbladder dye.

**DISORDERS OF PANCREAS.** Clinically, the symptoms of pancreatitis are so similar to those of gallbladder disease as to be practically indistinguishable. Probably the most important factor in making the diagnosis of pancreatitis is to keep in mind that such a condition may be present when one would ordinarily consider that gallbladder disease is the cause of the patient's complaints. In the acute exacerbations of chronic relapsing pancreatitis, the differentiation hinges primarily on finding an increased serum amylase at the onset of the attack. In the chronic phases of the disorder, the recognition of its presence will depend chiefly on the discovery of steatorrhea or diabetes mellitus or x-ray demonstration of calcification of the pancreas. Numerous studies have revealed that the classic picture of painless, progressive jaundice is not the most common form in which carcinoma of the pancreas presents itself. Jaundice occurs in about half the cases, upper abdominal pain with no definite pattern or constant form of radiation in a much higher percentage. In the absence of jaundice, diagnosis is sometimes suggested by the roentgenologic demonstration of deformity of neighboring structures by extrinsic pressure.

**DIAPHRAGMATIC (HIATUS) HERNIA.** In recent years, there has been a growing appreciation of the fact that diaphragmatic (hiatus) hernia may be responsible for a variety of clinical pictures, one of which is chronic indigestion. In the typical case, an overweight individual of middle age or over tends to have symptoms on assuming the recumbent position, or on leaning forward after a full meal. The herniation may be associated with a nondescript form of indigestion or may cause a more severe attack of pain, sometimes strongly suggestive of biliary colic, at other times identical in type and distribution with that due to angina pectoris or myocardial infarction. The diagnosis is established with certainty when an awareness of the possible existence of diaphragmatic hernia leads to confirmation by roentgenologic examination made with this condition in mind.

**DISORDERS OF THE SMALL INTESTINE.** When organic disease of the small bowel arouses recurrent attacks of abdominal pain of a type that may be considered to fall in the category of

chronic indigestion, the clue to the site of the trouble will come from the recognition of the significance of the localization of the pain in the region of the umbilicus. More exact definition of the lesion will depend primarily on x-ray examination, which should be carried out with more careful attention to the small intestine than is ordinarily given in a routine gastrointestinal series.

**CHRONIC DISEASE OF THE APPENDIX (RECURRENT OBSTRUCTIVE DISEASE OF THE APPENDIX).** In a small number of cases chronic disease of the appendix may be the basis for a persistent indigestion of either the early or the late postprandial type. Experimental observations have demonstrated that irritation in the colon or over the appendix may produce pain due to reflex peristaltic activity in the prepyloric region. However, the grounds which justify removal of the appendix in an effort to cure a chronic indigestion of otherwise undetermined origin are not easy to establish. The mere presence of continued pain and tenderness in the right lower quadrant has proved to be a fallacious guide to the diagnosis of chronic disease of the appendix. However, the repeated failure to demonstrate an appendiceal lumen by the rectal instillation of barium, when coupled with recurrent periumbilical colic followed by some tenderness over the cecum, is considered by many to constitute sufficient evidence for the removal of the appendix after renal and cholecystic disease has been ruled out. The generally accepted present view is that a diagnosis of recurrent obstructive appendiceal disease should be made only when a history of recurrent attacks of appendiceal colic has been secured, and, even so, the diagnosis does not become reasonably certain until evidence of appendiceal inflammation (localization of the pain in the right lower quadrant, tenderness and rigidity in McBurney's region, fever and leukocytosis) has occurred during one or more of the attacks.

**ORGANIC DISEASE OF THE COLON.** In most cases, organic disease of the colon is characterized by the appearance of one or a combination of the following symptoms: (1) Diarrhea or constipation, or both; (2) bleeding from the bowel; (3) abdominal pain. The following statements regarding disease of the colon are made primarily with respect to pain and the possibility that such pain may be interpreted by the patient to be "indigestion." The character of the pain is deter-

mined by the site of the lesion, the presence or absence of obstruction, and the extent to which neighboring structures are involved. In general, pain due to disorders of the colon is referred to the lower half of the abdomen, although lesions in the hepatic or splenic flexure may give rise to pain in the upper right and left quadrants of the abdomen, respectively, while lesions in the cecum frequently cause perumbilical pain not infrequently mistaken for appendicitis. Obstructive phenomena, which are relatively rare in disorders of the proximal part of the colon, are much more commonly produced by malignant growths of the left half of the colon, due to the frequency of fibrous annular lesions and the more solid contents of the colon in this region. Indigestion, frequently associated with nausea, is common, usually due to reflex disturbances in the stomach. The symptoms of the different organic diseases of the colon have so many features in common that exact diagnosis usually must rest on the results of the more precise methods of examination, the most important of which are x-ray and proctoscopic examination. Any symptom referable to the colon, particularly in an individual of 30 to 35 years or older, warrants a thorough investigation with the special aim of searching for a carcinoma. Particularly in the colon, but also in the stomach, a normal x-ray study does not rule out cancer. If symptoms fail to clear under therapy, the x-ray examination, like any other physical examination, should be repeated.

**INDIGESTION DUE TO FUNCTIONAL DISORDERS OF THE DIGESTIVE TRACT.** Several circumstances afford presumptive evidence of the functional origin of chronic indigestion: clear association of symptoms with states of fatigue or emotional stress, youth of the patient, duration of the illness over a long period of time, variability of symptoms, absence of serious deterioration of health. The diagnosis may be considered established, however, only when history and physical examination, laboratory data, x-ray examination, and, in appropriate cases, endoscopic examination fail to reveal organic disease, in or out of the digestive tract, that can logically explain the digestive symptoms. Even when the investigation has been carried out in the most thorough and expert manner, unavoidable error will occur in a small percentage of cases, and the passage of time will disclose organic disease not presently demonstrable. At times the clinical evidence in favor

of ulcer and the corollary data may be so impressive that a diagnosis of ulcer may be considered permissible in spite of negative x-ray findings. On similar grounds, a diagnosis of chronic gall-bladder disease may be reached even when cholecystography has yielded negative results.

Psychogenic factors, excessive use of tobacco, coffee, or alcohol, improper habits of eating, cathartic habituation—each one alone or in combination with the others may be responsible for the faulty functioning of the digestive tract. The symptoms vary widely, sometimes mimicking organic diseases involving the stomach or colon so closely that only after the most intensive survey and prolonged observation will it be possible to conclude that no structural disease of the digestive tract is present.

Even when demonstrable structural disease exists, the symptoms may be markedly influenced by coexistent, although less apparent, emotional disturbances. When no structural disease is found, one is not justified in assuming that psychogenic factors are responsible for the symptoms, unless the patient presents clear evidence of emotional disturbance. Mistakes will be minimized if one bears in mind that, though psychogenic disorders are a very common cause of indigestion, it is unsafe to make such a diagnosis in an individual case unless the evidence, both positive and negative, points unequivocally toward such a conclusion.

**INDIGESTION DUE TO FOOD INTOLERANCE.** Hypersensitivity to specific foods is a frequent cause of digestive symptoms, including indigestion of various types. In some cases, the constant association of symptoms with the ingestion of certain foods, even when the recipient is unaware that the offending foods are incorporated in the diet, the personal and familial history of an allergic background, the demonstration of positive skin tests and of antibodies that are capable of being transferred passively, the prompt cessation of symptoms on elimination of the offending foods from the diet, afford a chain of evidence that is incontestable. However, in a much higher percentage of cases, the proof that indigestion is caused or aggravated by a suspected food allergy rests on much more uncertain ground. This uncertainty is common to most disorders ascribed to an allergic reaction to foods. The immunologic tests may be negative, the provocation of symptoms by the offending foods may not be imme-

diate and clear-cut, and the harmful influence of the suspected foods may have no better support than the statement of the patient himself. In the absence of objective proof, it is frequently difficult or impossible to know how much a supposed food sensitivity is attributable to a genuine food intolerance and how much to the fears and suspicions of an apprehensive patient. When the intolerance to specific foods seems real, it is again a problem to decide whether the symptoms are due to their relative indigestibility or to their content of chemical irritants that may be more potent in some individuals than others, or whether an allergic reaction in the digestive tract is the basis of the disturbed function. The fact remains that, however obscure may be the precise mechanism by which these various food intolerances operate, there are frequent instances in which indigestion seems to be related to the specific effect of certain foods, varying in each individual case. In some persons food intolerance appears to be the sole cause of symptoms; in others it may exert its effects in conjunction with obvious psychogenic influences, while in still others the food intolerance may be expressed only when demonstrable organic disease is present.

Suspicion with regard to the allergic basis of the indigestion is aroused by a family history of allergy, or a personal history, in the past or present, of some unquestionably allergic disorder such as hay fever or asthma. Frequently the patient recognizes that certain foods such as egg or milk may be responsible for his symptoms but may be unmindful of the fact that these same foods are commonly used in the preparation of other articles of his diet.

For the detection of the offending foods, skin tests are so unreliable as to be usually valueless. More helpful information can be obtained from elimination diets, or from a careful, time-consuming history in which the patient is questioned regarding his experience with all the common articles of a dietary. Only by testing and retesting the effects of suspected foods is it possible to arrive at a reasonably clear conclusion as to the role which specific food idiosyncrasies are playing in the particular case. It should be emphasized again that the discovery of a food intolerance and the temporary relief of symptoms by elimination of the offending substance does not prove the absence of a concomitant organic disease. It is not uncommon, for example, for the indigestion

of chronic gallbladder disease to be considerably relieved or completely abolished for long periods of time, merely by eliminating the known food offenders.

**INDIGESTION DUE TO HYPOGLYCEMIA.** Occasionally indigestion may be an outstanding manifestation of hypoglycemia. Since the symptoms are due to increased motor activity in the stomach and are relieved by the ingestion of food, a picture suggestive of that caused by peptic ulcer may be produced. The origin of this form of indigestion may be suspected from the concurrent appearance of other phenomena characteristic of hypoglycemia, and the proof will depend on blood sugar studies and on radiologic findings demonstrating the absence of structural disease.

**GENERAL DIAGNOSTIC CONSIDERATIONS.** The introduction of more exact methods of diagnosis has brought about a steady diminution in the importance of the clinical picture alone, in arriving at a conclusion as to the nature of the specific disorder responsible for a malady. However varied may be the types of injury or stress, the response of the digestive tract and the resulting symptoms are relatively limited. Accurate information regarding the localization and projection of the pain and, hence, the cord segments affected by the sensory stimuli, affords an invaluable starting point from which one may consider the various structures that could be responsible for the symptoms. Additional data pertaining to the age and sex of the patient, duration of the illness, factors precipitating or relieving the symptoms, and accessory details narrow still further the diagnostic possibilities. In the main, however, a definitive diagnosis will rest chiefly on the results of x-ray or direct inspection of the affected organ. The similarity of symptoms produced by a variety of lesions in the same structure or in other structures innervated from the same cord segments makes diagnosis on clinical grounds alone a hazardous undertaking, particularly in the detection of disease in its early and most remediable stages. Reliance on x-ray or endoscopic examination must be tempered with a recognition of the shortcomings of even these methods of investigation; in some cases only microscopic examination of the suspected tissues can define the character of the morbid process.

Difficulties in ascertaining the primary site of a gastrointestinal disorder are frequently aroused by the reciprocal relationships between the upper

and lower digestive tract. Lesions in the upper tract, such as gallbladder disease or peptic ulcer, commonly give rise to reflex disturbance in the colon, and in some cases the symptoms referable to the irritable colon may preponderate to such an extent that they actually occupy the forefront of the patient's attention. Similarly, primary disorders in the colon may be associated with reflex alterations in the functions of the stomach, and indigestion, characterized by high epigastric distress, may be the predominant symptom, distracting the attention from the original site of the trouble.

**Procedure in Investigation of Chronic Indigestion.** The first step in the elucidation of chronic indigestion must cover the ground encompassed in every thorough initial examination: a painstaking and complete history and physical examination and the routine blood and urine tests. The results of this first survey and the additional special procedures that may be suggested by it will serve to indicate whether any organic disease can explain the symptoms of which the patient complains. In some cases, as in angina pectoris or myocardial failure, where the diagnosis is clearly established and the effects of therapy are quickly ascertained, further investigation of the digestive tract is unnecessary.

X-ray examination of the alimentary tract and gallbladder is the cornerstone on which the diagnosis of gastrointestinal disease is built; elaboration on the importance of this procedure is unnecessary. Lesions of the stomach and colon ordinarily are readily disclosed. The standard gastrointestinal series frequently fails to reveal the small intestine in adequate detail; special small-intestinal studies should be made when involvement of this structure is suspected.

The chief value of stool examinations is in the detection of occult blood. The persistence of bleeding in a case of gastric ulcer that is being properly treated arouses the strong presumption that the lesion is malignant.

Gastric analysis no longer occupies a position of importance in the diagnosis of disorders of the stomach and duodenum. Normal individuals exhibit variations in the acidity of gastric juice that may range from complete absence of hydrochloric acid to high figures that tend to overlap those seen in disease. Moreover, aside from the measurement of the volume and acidity of the gastric juice, the information afforded by the various

special test meals is ascertained more easily and accurately by x-ray examination. Nevertheless, with appreciation of its limitations, gastric analysis continues to be employed as a procedure that provides data that may be of assistance in cases where the x-ray evidence is equivocal.

Fasting gastric juice of large volume and high concentration of acid is an almost constant finding in the presence of duodenal ulcer. In benign gastric ulcer, the volume and the level of acid concentration tend to be lower, but acid is never completely absent. Anacidity, particularly after the administration of histamine, bespeaks strongly of the malignant character of a gastric ulcer. Free acid does not, however, rule out malignant disease of the stomach. In cases of pernicious anemia, in which indigestion may be the presenting symptom, anacidity refractory to histamine is invariably present.

Proctoscopic examination is indicated in most conditions suggestive of organic disease of the colon, and is obligatory when there is any suspicion that cancer of the rectum exists.

Gastroscopy is useful in the determination of the completeness of healing of an ulcer and in disclosing lesions unseen by x-ray, notably hemorrhagic and ulcerative gastritis. It may reveal fungating or bulky lesions which are obviously neoplastic, but these can usually be diagnosed with less discomfort by barium study. Absolute recognition as to the nature of ulcerative or bulky lesions is impossible since biopsy cannot be obtained, but a better conjecture can be made after both gastroscopic and x-ray studies than by either alone.

Finally, when organic disease of the digestive tract has been excluded and the possibility of an allergic disorder is entertained, elimination diets should be employed.

The question of procedure in the investigation of chronic indigestion in a patient on the wards of a large teaching hospital or at a diagnostic clinic poses no difficult problems. All the methods mentioned above may be employed; under these circumstances the patient expects and usually submits to any examination that will throw light on his illness. The problem is different in private practice away from such institutions. A high percentage of gastrointestinal disorders seen in patients who make up the practice of the average physician are of functional origin. To subject all persons complaining of indigestion to an imme-

diate routine survey involving all of the indicated procedures would be difficult, if not impossible, from the standpoint of expediency and expense. On the other hand, the alert physician must be constantly aware of the fact that any compromise with thoroughness inevitably exposes the patient to the risk of losing the opportunity, possibly an irretrievable one, of discovering an early and curable malignant disease. For the average physician in private practice, this dilemma is well-nigh insoluble, and its evil consequences can be mitigated only by recognition on the part of both patient and physician of the difficulties inherent in the problem.

### DYSPHAGIA

Difficulty of swallowing may be classified according to the three chief mechanisms causing this symptom.

1. Dysphagia due to mechanical obstruction in the esophagus
2. Dysphagia due to disturbance in the neuromuscular mechanisms of swallowing
3. Dysphagia due to lesions of the mouth, pharynx, or larynx, causing pain or mechanical hindrance to passage of food into the esophagus

**Dysphagia Due to Mechanical Obstruction in the Esophagus.** This group is by far the most important and comprises 90 per cent or more of all cases of dysphagia.

**CARCINOMA.** This is the most common lesion causing mechanical obstruction in the esophagus and is responsible for 50 to 60 per cent of all cases in which the complaint is dysphagia. The condition occurs far more frequently in men than in women, usually in patients over 50 years of age. The first and most important symptom is difficulty in swallowing, usually of gradual onset, sometimes sudden, progressing steadily until softer foods, and then liquids, are unable to pass the stricture. Regurgitation and pain are usually inconspicuous or absent. X-ray examination usually reveals an irregular obstruction, with relatively little dilatation of the esophagus above. Diagnosis is made certain by esophagoscopy and obtaining bits of tissue for microscopic analysis.

**CARDIOSPASM.** This condition is found in about 20 per cent of all cases of dysphagia. The cause is

not known but is generally attributed to a failure of relaxation of the cardiac sphincter. The majority of cases begin in early adult life, the onset being either gradual or sudden, with either pain or dysphagia as the first symptom. Dysphagia is usually transitory, with variable intervals of practically complete freedom from this symptom intervening. Gradually, over a period of years, the difficulty in swallowing becomes more persistent and severe. Pain and regurgitation are common, the latter frequently taking place during the night and causing aspiration and infection of the respiratory tract. Aside from the history, diagnosis is made from the characteristic x-ray findings: a smooth constriction at the terminal portion of the esophagus, with more or less conspicuous dilatation above.

**BENIGN STRICTURE.** In strictures following the ingestion of lye or other corrosive chemicals, and in those associated with scleroderma, the relationship is clear. In many, however, the cause is unknown and the history is practically identical with that seen in carcinoma. X-ray usually reveals a smooth constriction, most commonly in the upper or middle portions of the esophagus, with little or no dilatation above. When the symptoms have lasted more than 18 months or 2 years, the differentiation from carcinoma is usually not a problem, since patients with untreated carcinoma rarely survive this period of time. When the symptoms are of short duration, differentiation from carcinoma may be difficult or impossible without esophagoscopy and biopsy.

**PHARYNGOESOPHAGEAL DIVERTICULUM.** This is a relatively uncommon cause of dysphagia. The pouch projects from the hypopharynx just above the opening of the esophagus. As the pouch enlarges and sags, because of the weight of its contents, it tends to occlude the esophagus. The characteristic symptoms are dysphagia and regurgitation of food that has become trapped in the pouch. The appearance on x-ray examination is diagnostic.

**FOREIGN BODIES.** Usually the history discloses the possibility that such an accident has occurred. Pain with each swallow and dysphagia are the outstanding symptoms. X-ray is sometimes of value in the diagnosis. In some doubtful cases, esophagoscopy is essential.

**EXTRAESOPHAGEAL LESIONS.** Rarely, dysphagia is caused by extraesophageal disorders such as carcinoma of the thyroid, aneurysm of the

aorta, mediastinal tumors, and diaphragmatic hernia.

**Dysphagia Due to Disturbance in the Neuromuscular Mechanisms of Swallowing.** In the act of swallowing, food is transferred from the oral cavity to the esophagus by contraction of the tongue against the hard palate, by the action of the pharyngeal constrictors, and by the relaxation of the pharyngoesophageal sphincter. Food is thereby prevented from being forced into the nasopharynx, and it fails to enter the larynx by virtue of the elevation of this structure beneath the protective cover of the base of the tongue. Dysphagia results when any part of this coördinated and complex series of movements is disturbed. The features witnessed in varying degree in these disorders are difficulty in maneuvering food into the esophagus in the absence of pain or mechanical hindrance, regurgitation of fluids through the nasopharynx, aspiration of food into the larynx, nasal character of the voice, and weakness of the palate. The most common examples of this type of dysphagia are *myasthenia gravis*, *bulbar palsy*, *diphtheritic polyneuritis*, *acute bulbar poliomyelitis*, *cerebral vascular accidents*, and *botulism*. The *Plummer-Vinson syndrome* may also be listed here since the difficulty of swallowing in this condition resembles that due to a neuromuscular disorder, although the actual cause of the dysphagia is not entirely clear. The patients are middle-aged women who present the characteristics of a chronic idiopathic microcytic anemia in conjunction with signs of vitamin-B complex deficiency. The cause of the disorder is not known. According to one viewpoint, the basis is a psychogenic one leading to a nutritional deficiency, primarily of iron and vitamin B. The dysphagia is attributed to atrophic changes in the pharynx, possibly associated with disturbances of the intrinsic nervous apparatus in the pharyngeal wall.

**Dysphagia Due to Lesions of the Mouth, Pharynx, or Larynx, Causing Pain or Mechanical Hindrance to Passage of Food into the Esophagus.** In most cases the cause of trouble in this group is obvious, and detailed consideration of the various lesions is unnecessary; peritonsillar abscess and an infiltrating carcinoma of the tongue are examples.

**Differential Diagnosis.** A common complaint, not to be confused with dysphagia, is *globus hysterius*, which occurs practically always in

neurotic patients, and under conditions of nervous tension. The complaint is usually of a lump or sense of constriction in the throat that cannot be dissipated by swallowing. No real difficulty of swallowing is experienced.

Differentiation between the common disorders of the esophagus is not infrequently very difficult. Cancer of the esophagus sometimes presents a sudden rather than gradual onset, and the roentgenogram may have the smooth, symmetric appearance more commonly seen with benign stricture or cardiospasm; even esophagoscopy and biopsy may be inconclusive.

Certain symptoms associated with dysphagia have diagnostic value. Hiccough, together with difficult swallowing, indicates a lesion at the terminal portion of the esophagus, such as carcinoma, cardiospasm, or hiatus hernia. Dysphagia, followed after an interval of some duration by hoarseness, usually means extension of a malignant growth beyond the walls of the esophagus and the involvement of a recurrent laryngeal nerve. When the hoarseness comes first and the dysphagia later, the primary lesion is almost always in the larynx. Coughing with each swallow of food or drink means a fistulous communication between the esophagus and trachea. Coughing occurring some time after swallowing may be due to regurgitation of food, most common in cardiospasm and pharyngeal pouch.

**Procedure.** Examination of the mouth and pharynx should disclose those lesions the effect of which is to impede the transfer of food from the mouth to the esophagus, either because of pain or mechanical interference. When lesions of the hypopharynx (e.g., chronic abscess secondary to tuberculosis of the spine) or of the larynx (e.g., tuberculosis or carcinoma) are suspected, examination with a mirror is necessary.

The investigation of mechanical obstructions in the esophagus is accomplished mainly by x-ray examination and, in doubtful cases, by esophagoscopy and biopsy of the suspected tissue. Barium mixtures should not be used in cases of suspected foreign body, since the latter may be obscured; nor should a thick barium mixture be employed when the history indicates the presence of an almost complete obstruction, since complete occlusion may be precipitated. In cases of obstruction at the cardiac orifice, a large thick-walled stomach tube should be introduced; if the tube enters the stomach without difficulty, car-

diospasm may be assumed to be present; otherwise, a benign or malignant stricture is responsible for the obstruction.

When a neuromuscular disturbance of the pharynx is thought to be the cause of dysphagia, this can be demonstrated most readily by fluoroscopic examination. When barium mixture is swallowed, some of the opaque material will be seen to cling to the pharyngeal walls and in the pyriform sinuses, and almost invariably a small amount of the barium will trickle into the trachea. If there is question of myasthenia gravis being present, a mixture of 1.5 mg. neostigmine and 0.6 mg. atropine is given subcutaneously, which should bring about very striking relief of dysphagia within 30 minutes in cases of myasthenia gravis, and little or no improvement in the other forms of neuromuscular dysphagia.

### NAUSEA AND VOMITING

**General Principles.** Nausea and vomiting may each occur independently, but they are usually so closely allied that they may be conveniently treated as one symptom. Commonly, nausea precedes vomiting. The physiologic basis for this symptom appears to be a diminution in the functional activity of the stomach and alterations in the motility of the duodenum. The gastric mucosa becomes pallid and the tone, motor, and secretory activity of the stomach are all decreased. In addition, alterations in the motor activity of the duodenum have also been described as being constantly present. Other evidences of autonomic activity are the frequent association of pallor of the skin, increased perspiration, salivation, and the occasional association of hypotension and bradycardia (vagal stimulation). Anorexia is also present, and it is assumed that the loss of appetite and nausea are devices developed in the course of evolution to protect the organism against the ingestion and absorption of harmful materials.

Vomiting is a more complicated symptom, depending on the coöordinated activity of a number of structures: closure of the glottis, contraction and then fixation of the diaphragm in the inspiratory position, closure of the pylorus and contraction of the antrum of the stomach with relaxation of the rest of the stomach including the cardiac orifice, and contraction of the abdominal muscles. It is the latter act that is primarily responsible for the expulsion of the gastric

contents, the stomach playing a relatively passive role. When vomiting is prolonged and forceful, reverse peristalsis in the small intestine may force bile-stained duodenal contents, or even material from lower levels of the small bowel, into the stomach.

These various activities involved in the act of vomiting are controlled and coördinated in the proper sequence by the vomiting center, a small area in the dorsal nucleus of the vagus which receives afferent stimuli from all parts of the body, and which, under certain conditions, sends out efferent stimuli to the appropriate structures: larynx, diaphragm, stomach, abdominal muscles. Afferent vomiting stimuli fall into two main groups: those that act primarily by enhancing the activity of the vomiting center, and those that arise in peripheral parts of the body and are then conveyed to the vomiting center. These two modes of stimulating the organism to vomit have been responsible for the separation of "central" from "reflex" vomiting, although the researches of Hatcher have shown that all vomiting is in reality of reflex nature. Subthreshold stimuli are constantly streaming from all parts of the body to reach the vomiting center. Vomiting takes place under two circumstances: either the stimuli from some region in the body are intensified to the threshold level ("reflex" vomiting), or the sensitivity of the center itself is raised to a point at which it responds to the ordinarily ineffective impulses reaching it ("central" vomiting). Hatcher's investigations have also disclosed the fact that some substances exert their chief effect through influences on the heart. Thus the vomiting that is witnessed when the physiologic dose of digitalis has been exceeded has been found, experimentally, to be due to reflexes arising from the heart, although the validity of this concept has been questioned by subsequent work.

Probably all sensory nerves, cranial and peripheral as well as autonomic, are capable of transmitting emetic impulses. Any stimulus, if sufficiently painful, may be associated with nausea and vomiting: the "sickening" pain of a blow to the testis is an example. In the abdomen, afferent stimuli are carried by the vagus nerves and the sympathetics. Experimental work on structures subserved by both sets of nerves shows that the vagi are the more important in this respect. Cortical stimuli as a result of psychic disturbances, disagreeable sights, odors, or tastes,

stimuli from the labyrinth and pharynx, as well as impulses from the digestive and biliary tracts, peritoneum, urinary and pelvic organs, are common causes of nausea and vomiting. In addition, vomiting may result from the action of drugs and poisons introduced into the body, as well as from toxic substances generated in the organism. In this latter category are the "toxins" of acute infectious diseases and, presumably, the retention products responsible for the vomiting of uremia. It is possible that abnormal metabolites may play a role in the vomiting accompanying other metabolic disorders such as diabetic acidosis, the crises of thyrotoxicosis, and conditions associated with functional impairment of the liver. In hyperparathyroidism, the abnormal elevation of the level of ionized calcium in the serum and the loss of sodium and extracellular fluid, with the consequent development of uremia, are probably important in the production of nausea and vomiting.

Although the general principles concerned with the mechanism of vomiting appear to be clear, the precise application of these principles in the elucidation of vomiting as it appears in specific clinical conditions is not always possible. In many instances multiple factors may be operative, and it is difficult to estimate the part played by each. In others, the stimuli to vomiting are unknown, and we are uncertain whether their effect is peripheral or central. Vomiting is a common phenomenon in congestive heart failure, but how much is due to engorgement of the digestive organs, how much to reflexes from the heart, and how much to cerebral anoxia is impossible to state. It is usual to assign the vomiting of acute infectious diseases to the action of toxins on the medullary center, yet it has been demonstrated that *staphylococcus* enterotoxin acts mainly on the sensory nerves of the digestive tract rather than on the vomiting center. Vomiting frequently occurs early in diabetic acidosis; once again we are unable to state with assurance whether this is due to functional derangements in the digestive tract or to central stimulation, presumably by abnormal metabolites. The same problem exists with regard to cirrhosis of the liver and other conditions characterized by disturbed liver function. The cause of vomiting in uremia is still a matter of conjecture. In part, it may be due to the irritating influence on the gut of the large quantities of ammonium salts converted by bacterial action from the abnormally large quanti-

ties of urea present in the secretions; in part, it may be due to the central effect of guanidine and other, as yet unknown, substances retained in the blood. Further enumeration of the uncertainties of our knowledge is unnecessary to stress the point that in many clinical conditions the mechanism of vomiting is complex and imperfectly understood.

There is one form of vomiting that occurs in conditions associated with increased intracranial pressure that is quite distinctive—the so-called projectile vomiting. This is characterized by a sudden unexpected and sometimes violent ejection of gastric contents. The reason for its chief peculiarity, absence of nausea, is unknown.

**Effects of Vomiting.** Like any condition accompanied by profuse loss of water and salts, excessive vomiting may lead to a state of deficiency in the extracellular fluid volume (Chapter 28) and the plasma volume, and hence to acute peripheral circulatory failure (Chapter 14). However, vomiting is distinctive in that the loss of chloride is greater than the loss of base. Normally, hydrochloric acid is formed in the stomach by removing the chloride ion from the blood. When, as the result of vomiting, there is excessive loss of hydrochloric acid from the body, a characteristic chemical pattern develops in the blood. This is characterized by deficiency of chloride and excess of bicarbonate (formed from the base no longer balanced by chloride) and elevation of the non-protein nitrogen as the result of prerenal deviation (Chapter 19). This chemical pattern is most typically seen in persons with intestinal obstruction, but may be observed whenever there is excessive vomiting.

**Classification.** Vomiting is so protean a manifestation of bodily dysfunction, and its mode of origin so uncertain in many disorders, that a simple, logical classification, according to either mechanism or etiology, is impossible. The one given below has no special merit and serves only as a basis for brief comments on certain specific conditions.

**ACUTE INFECTIOUS DISEASES.** Nausea and vomiting may be encountered at the onset or during practically any acute infection of a severity sufficient to cause the usual constitutional symptoms. This is particularly prone to occur in children and when the infectious process is one primarily involving the gastrointestinal tract, the

liver (e.g., acute infectious hepatitis), or the meninges (in the latter case, the vomiting may be of the projectile type).

**ACUTE ABDOMINAL EMERGENCIES ("SURGICAL ABDOMEN").** All the various disorders that fall into this category, and that need not be enumerated, are associated with nausea and vomiting. When the biliary tract is involved, these symptoms are far more intense in obstructions of the common duct than when the gallbladder alone is affected. In general, the most severe and persistent vomiting is seen in acute peritonitis and in acute obstructions of the small bowel (including paralytic ileus—Chapter 4).

In certain cases of acute appendicitis, pain may be minimal and vomiting outspoken, although the reverse relationship is more common.

**CHRONIC INDIGESTION.** Nausea and vomiting may be components of the chronic indigestion resulting from almost innumerable causes. Spontaneous and frequent nausea and vomiting are uncommon in uncomplicated peptic ulcer; more often, vomiting is induced by the patient to relieve pain. The regular appearance of nausea and vomiting of copious quantities of material a number of hours after eating indicates the presence of pyloric obstruction due to either a benign or a malignant lesion. Unexplained nausea and loss of appetite may be the earliest symptoms of a carcinoma of the stomach or of almost any type of diffuse disease of the liver.

**DISEASES OF THE HEART.** Congestive heart failure is frequently associated with nausea and vomiting which may be the chief complaints of the patient. Under such circumstances these symptoms may result from drugs (more especially from digitalis, opiates, and xanthines), from congestion of the abdominal viscera, from the frequently associated uremia, or from progressive myocardial disease. These symptoms are often present in acute myocardial infarction and in severe forms of diphtheritic myocarditis, and it is probable that in these cases the symptoms arise, in part at least, from reflexes originating in the heart.

**METABOLIC DISORDERS.** During the crises of hyperthyroidism, in acute hyperparathyroidism, in the course of Addison's disease (especially during the acute phases), and at the onset of diabetic acidosis, nausea and vomiting may be prominent symptoms. Anorexia and, less commonly, vomiting may result from disorders of the pituitary

gland (Simmonds' disease). The cyclic vomiting of childhood is believed by some to be allergic in origin; others consider it to be caused by acidosis. The familiar morning sickness of the early weeks of pregnancy is listed here because there is some evidence that this phenomenon, so frequent as to be considered physiologic by some, is due to endocrine metabolic alteration initiated by the implantation of the fertilized ovum. Actually, the cause of the early vomiting of pregnancy is unknown. Various hormones and types of metabolic disturbances have been incriminated; no hypothesis has won general acceptance. Psycho-genic factors undoubtedly play a role in some cases, and in the more severe forms (pernicious vomiting of pregnancy) there are superimposed additional causes of vomiting due to the effects of the prolonged vomiting itself: starvation, dehydration, etc. Reference has already been made to the sometimes severe and persistent nausea and vomiting of uremia, which are to be differentiated from the somewhat similar manifestations that may occur in acute nephritis or hypertensive disease without nitrogen retention (pseudouremia). In this latter condition the symptoms have long been considered to be due to cerebral edema or spasm of the cerebral vessels; in some cases the symptoms are actually due to thrombosis in the cerebral vessels.

**DISORDERS OF THE NERVOUS SYSTEM.** Menigitis, migraine, and tabetic crises are associated with nausea and vomiting, sometimes severe and prolonged. The projectile vomiting caused by lesions associated with increased intracranial pressure has already been mentioned. The coexistence of nausea, vomiting, and well-marked vertigo is suggestive of a labyrinthine disturbance such as occurs during seasickness, airsickness, and the characteristic seizures of Ménière's syndrome.

**DRUGS AND POISONS.** Since the majority of these substances are capable of inducing vomiting which subsides after withdrawal of the offending substance, detailed comment is unnecessary.

**PHARYNGEAL IRRITATION.** A prosaic but common and sometimes disturbing cause of morning vomiting is the irritating effect of a postnasal discharge.

**PSYCHOGENIC VOMITING.** This term is applied to the nausea and vomiting that may occur as transitory phenomena, the result of some emotional upset, or persistent as a consequence of a more profound psychic disturbance. The condi-

tion known as anorexia nervosa, in which, as the result of an emotional disturbance, the patient may suffer from a profound loss of appetite and may vomit after every meal with consequent rapid weight loss, constitutes one example of this type of vomiting. More commonly, patients with emotional disorders and vomiting maintain a relatively normal state of nutrition, because only a relatively small fraction of the ingested food is vomited.

**Differential Diagnosis.** Vomiting is to be differentiated from regurgitation, which implies the expulsion from the esophagus of undigested food retained because of some obstruction such as occurs with cardiospasm or esophageal diverticulum, or the expulsion of gastric contents without preceding nausea. Regurgitation is caused by the intrinsic activity of the esophagus or stomach, and is not accompanied by the forceful contraction of the abdominal muscles (retching) that characterizes vomiting.

The character of the vomitus and the circumstances under which vomiting occurs are sometimes of importance in estimating the significance of this symptom. When several hundred milliliters of material are regularly vomited a number of hours after the preceding meal, and particularly when particles of undigested food can be recognized, pyloric obstruction is a practical certainty. If this vomitus contains free hydrochloric acid, the obstruction may be due either to ulcer or to carcinoma; absence of free hydrochloric acid suggests a malignant growth. Fecal odor after protracted vomiting indicates the presence of low obstruction of the small bowel, or of peritonitis. Streaks of blood have no significance. Large quantities of blood, either bright red, or dark brown when it has been chemically altered by the acid of gastric juice, usually denotes an intragastric lesion or a ruptured esophageal varix. Bile is commonly present in the gastric contents whenever vomiting is prolonged. It has no significance unless constantly present in large quantities, when it may signify an obstructive lesion below the ampulla of Vater.

In general, nausea and vomiting due to lesions or functional derangement of the stomach bear some definite relationship to eating. Unfortunately, this statement is less helpful than would appear at first glance. Indigestion, associated with nausea and vomiting, especially occurring shortly after eating, may be caused by a func-

tional disturbance of the stomach dependent on an obscure lesion such as a chronic infection in the urinary tract or pelvic organs. Vomiting which relieves an epigastric pain of the late post-prandial type suggests the presence of an ulcerative lesion in the stomach or duodenum. Vomiting during the night, with expulsion of clear, acid-containing gastric contents, and with relief of epigastric pain, is common in duodenal ulcer, and is due to the continued nocturnal hypersecretion that takes place in this condition.

Vomiting which is entirely unrelated to eating is often due to exogenous (drugs) or endogenous (uremia, hepatic and diabetic coma) intoxication, to disorders of the nervous system, or to the various metabolic disturbances which have been mentioned. Vomiting occurring before breakfast in a young woman is commonly due to pregnancy.

Nausea and vomiting are symptoms too widespread to be investigated by any definite program of study. In most cases the associated symptoms are of more value in defining the cause of the underlying disorder. It may be well, however, to mention some of the conditions in which the cause of the nausea and vomiting may not be readily apparent: carcinoma of the stomach in an early stage, chronic indigestion due to lesions remote from the stomach, diabetic acidosis, uremia, Addison's disease, pregnancy, tabetic crises, migraine when the headache is brief and overshadowed by the nausea and vomiting, acute hepatitis at the onset and before jaundice appears, or the acute epidemic infectious disease whose only manifestation is nausea and vomiting (epidemic nausea and vomiting).

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## 16

### Constipation and Diarrhea

William Dock

Constipation  
Diarrhea  
Chronic Diarrhea

Constipation is evidenced by failure to move the bowels with the customary frequency, or by the passage of rare, small, hard, and perhaps painful masses. Diarrhea is present when movements occur with abnormal frequency and the total daily bulk is abnormally large, the movements watery, foamy, mucoid, or blood-tinged. These derangements of colonic function may be due to trivial or serious disorders; both are frequent occurrences in people of all ages, and the two conditions may alternate in the same patient. Discomfort in the abdomen often precedes, and painful anal spasm may follow, the diarrheal movements; patients with constipation may experience fullness or pain in the epigastrium after meals, and aching pain in the perineum after passage of large, hard fecal masses. Systemic symptoms may be absent in both disorders, or there may be weakness, aching of muscles, headache, indigestion, belching, and even associated discomfort on urination. The causes of constipation or diarrhea may be improper diet, local organic disease, systemic disease, or disturbances of the personality and emotions.

Splitting of foodstuffs, and their absorption into the body, takes place largely in the jejunum, and is so nearly completed in the ileum that only a small amount of fat, fatty acid, and protein, together with some starch and all the cellulose and lignin, reach the cecum. Though bacteria split the polysaccharides in the colon, little or none of the resulting pentose or hexose is absorbed. The main function of the colon is water and electrolyte reabsorption, and, in civilized people or trained beasts, the storage of the feces. Some proteins, such as uncooked egg albumin, are poorly digested; so are some poorly cooked starches, as in legumes. These give rise to unusually abundant bacterial growth and colonic gas production. When the colon is resected, the water-reabsorptive function of the ileum gradually increases, and the ileal residue at the terminus may closely resemble the normal stool. Infants and household pets are trained to restrict the occasions for defecation. Most adults and children have one or two movements, usually after breakfast or after the largest meal of the day. People who eat and sleep at irregular hours often have irregular bowel habits. Travel or disturbances in living habits usually cause temporary cessation of bowel movements.

In constipation the stools may be normal; they may be hard pellets, coated with mucus; or they may be voluminous cylinders followed by unformed or even watery material in those patients who have cathartic addiction. Normal stools contain fat when patients use much cream, butter, or vegetable oil; they contain bubbles when the diet has been rich in poorly cooked starch. The amount of fat and the foamy character are greatly increased in fermentative diarrhea due to pancreatic or jejunal dysfunction.

Defecation is due to mass peristaltic activity in the large bowel, and these peristaltic "rushes," which fill the sigmoid and rectum, produce the perineal sensations which, if voluntary inhibition is not exerted, cause relaxation of sphincters and increase of intraabdominal pressure by holding the breath and contracting the belly wall and diaphragm. Subconsciously, the individual can distinguish between rectal filling due to gas, leading to passage of flatus, and filling with feces. Loss of sensory acuity in the perineal region causes constipation and impaction of feces in the rectum; if there is an associated loss of sphincter tone, involuntary bowel movements occur.

The mass peristaltic movements of the colon are easily disturbed. They may be inhibited and the rectum and sigmoid remain empty, while the rest of the colon becomes distended for days at a time. This occurs during febrile illness, after injury or operation, or when the rushes (occurring at awkward times) have not been allowed to cause defecation. Lack of food or confinement, as in jails or small boats, may thus inhibit peristaltic activity for many days. This also occurs during emotional crises, and with the depressive psychotic states.

The frequency of these peristaltic rushes may be augmented by the manic emotional states, by hyperthyroidism, and by fear or anxiety. Increase in bulk of the material entering the cecum, increase in amount of chemically irritant content of this material, and inflammation of the ileum or colon also increases the frequency and the violence of the mass peristaltic episodes driving the fecal content into the rectum. If the sensitivity of the rectum is normal, or increased as a result of irritation, almost uncontrollable desire to defecate occurs, and the patient has diarrhea. However, all of the disorders, including the most severe inflammations which usually

cause diarrhea, may fail to do so in some patients. Patients may die with ulcerative colitis, never having had diarrhea; they may die of cholera, with the gut hugely distended with fluid, without having had any desire to defecate. If peristaltic rushes end above the sigmoid, or even before the rectosigmoid junction; or if the rectum is insensitive and the anal sphincter spastic, constipation occurs even when the bowel is inflamed and fecal material abundant.

Reabsorption of fluid occurs in the colon. When peristaltic waves are vigorous and defecation frequent, the movements are watery because of rapid passage from cecum to rectum; but even the inflamed or ulcerated colon can reabsorb fluid if passage is slow, or filling of the rectosigmoid difficult. Functional spasticity and stenotic lesions in the region of the sigmoid or rectum may be associated with constipation and diarrhea, alternating in phases of two to six days. This occurs with annular carcinomas, endometriosis, and granulomatous lesions such as those of lymphogranuloma venereum. When the lesion involves many inches of the rectum, frequent small watery movements or involuntary escape of such material may result.

**Constipation.** This may occur as acute episodes, easily explained by changes in diet, mode of life, or emotional tension, or as the outstanding or initial manifestation of organic disease of the bowel, or of a systemic disorder. Most frequent of all is habitual constipation, present for years or decades. Almost invariably this is linked in the patient's mind with abdominal discomfort, anorexia, headaches, or lassitude. In such patients use of laxatives, enemas, or purgatives has usually become a habit.

Some of these patients merely have exaggerated notions of the proper volume of the stools and use laxatives whenever the stool seems small or when they feel out of sorts. The need for this may have been impressed on them in childhood; it is constantly reiterated by press and radio. In other cases there has been "overtraining," with inhibition of rectal sensation or of peristaltic rushes, so that movements actually are infrequent. In the latter case, the stools are unusually firm and sometimes painful. Hemorrhoids, anal fissures, and fecal impaction may complicate this type of constipation, and these secondary effects

of faulty bowel habits increase the patient's fear of defecation.

In chronic constipation a complete history of eating habits, bowel habits, and a careful examination of the sphincter tone and condition of the anus and rectal mucosa are necessary in order to undertake management, which may include changes in diet, reeducation, local treatment of the secondary lesions, and the use of bland bulky materials such as paraffin oil, vegetable mucins, or agar. In many elderly patients, even the use of laxatives may be permitted in order to secure comfort for those who cannot be reeducated. In patients under 60, it is usually possible to cure cathartic habit, or constipation, by reeducation and diet alone.

In constipation without organic lesion, a spastic colon, or at least a spastic sigmoid, is not uncommon. Such a condition may exist without constipation, or with occasional bouts of mucous diarrhea, and the spastic colon, often associated with diverticulosis, is frequently accompanied by lower abdominal pain, diverticula, or postprandial distress closely simulating peptic ulcer in periodicity. Many of these cases seem to be bowel neuroses, associated with emotional instability or environmental stress. Even in these, however, food sensitivity is often an important factor, vaguely suspected by the patient. If coffee, chocolate, eggs, milk, and wheat are withheld, all symptoms may subside rapidly; other foods may also be factors. Skin tests are of no value; the history and elimination diets must be relied on for diagnosis. In some cases the trouble is seasonal and due to excessive ingestion of fresh fruit, tomatoes, or melons. Some patients, greatly benefited by diet, experience recurrences in spite of diet, when business or family troubles become pressing.

Thus constipation of functional type may be due to a variety of factors, alone or in combination. Management is based on the facts brought out by the history, on the character of the stools, and on the flaccid or spastic state of the anal ring, and the colon itself. In megacolon, with the most massive fecal retention, signs of systemic disturbance may be absent, and proof of auto-intoxication resulting from constipation is so weak that patients must be reassured on this score in order to combat the effect of advertisements dealing with this subject. Megacolon nearly always develops in childhood, and in some

cases seems to be due to congenital absence of the myenteric plexus in a part of the sigmoid which remains constantly in tone. In other cases the rectum fills, but anal sensitivity is lost, either because of neurosis or because of a defect in structure.

When constipation is recent and progressively severe, a serious psychogenic or organic cause must be suspected. Occasionally, the cause is found to be fistula or fissure in ano, or rectal ulceration, even though no perineal distress has been noted. More rarely, urinary tract disease is manifested first by constipation, but the converse relation, dysuria due to constipation or a rectosigmoid lesion, is more common. Complete obstipation due to fecal impaction is most commonly observed in elderly bedridden patients, and may be the initial complaint in patients with disorders of the central nervous system, such as diabetes, wasting disease, and tabes. In any event, recent constipation, and even habitual constipation, must not be dismissed as trivial or managed by trial of therapy without proper study. Such cases provide an opportunity for case finding in both psychogenic and organic disease. Tuberculosis, cancer of the cervix, prostatism, heart disease, involutional psychosis, as well as cancer or chronic inflammatory disease of the rectum or colon, must all be deliberately ruled out.

**Diarrhea.** Just as constipation of the habitual type is the predominant digestive disorder in urban civilization in the temperate zone, acute diarrhea is the common disorder among primitive and tropical peoples, and in military life. It was, until recently, a leading cause of death in infancy in North America, and still is throughout most of the world. Included in the acute diarrheal diseases are those due to salmonellosis, cholera and *Shigella* dysentery, amebiasis, schistosomiasis, and staphylococcal food poisoning. All these may produce severe prostration and even death. However, in cities with adequate sanitation, most acute diarrhea is due to abuse of cathartics, to ingestion of irritant food, or to trivial upsets such as nervous indigestion, acute febrile illnesses, or simple fatigue. Such bouts are particularly frequent in hot weather. Epidemics and occasional sporadic instances of *Salmonella* or viral enteritis also occur in infants and in adults, and institutional outbreaks of *Shigella* dysentery and amebiasis still occur in American cities.

Recurrent or chronic diarrhea may follow acute infectious dysentery, or may first manifest itself as a bout of diarrhea in a patient who rarely has had any bowel disturbances. Because acute nonspecific diarrhea is frequent, and is not to be distinguished clinically from the other types, management must be undertaken in most cases before an etiologic diagnosis can be established, and intensive diagnostic study usually proves to be unnecessary.

Diarrhea is due to frequent vigorous peristaltic rushes in the colon, usually associated with increased sensitivity of the anorectal zone. In infants and children this usually occurs, along with anorexia and vomiting, at the onset of acute exanthemas, respiratory infections, or even with car sickness or seasickness. In some adults this pattern persists, and every illness and every disturbance of the emotional life may cause diarrhea. Thus chronic looseness of the bowels may be the outstanding manifestation in an occasional instance of hyperthyroidism, digitalis toxicity, or pernicious anemia, to name only a very small number of conditions which cause this disorder as a nonspecific symptom.

As in so many diagnostic problems, the line of investigation will be determined by the discovery that an acute episode is merely an incident in a recurrent disorder lasting perhaps for decades; or, on the other hand, that the patient's case is only one of a series occurring in the community. If the disease is recurrent, study of the personality and of food sensitivity usually is more informative than examination of the stools, proctoscopy, or roentgen study of the gastrointestinal tract. In epidemics, the study of a particular source of food, as well as of the stools and of material obtained by proctoscopy, is of immediate value in determining etiology. When diarrhea does not clear up in two days of starvation, with replacement of water and appropriate electrolytes, and there are no other known cases of similar character, an immediate complete investigation is in order; this is also true in all cases of subacute or chronic diarrhea of insidious onset. Such an investigation during the first day or two of simple diarrhea is usually unnecessary, may further exhaust the patient, and rarely reveals anything significant.

In nearly all cases, even including cholera, the disease can be controlled by prompt physiologic management. During the first day or two the patient should take by mouth only hot tea or cool water, in small sips. If vomiting occurs it may be best to withhold fluid, and even to put down a Wangensteen tube for gastric drainage. Balanced mineral solutions (see Chapter 28), glucose, and—in severe collapse—plasma may be given to control dehydration and thirst. Such a therapy, even in brief self-limited bouts, greatly speeds recovery. Well-cooked rice, applesauce, and even well-cooked meat may be given when the patient has gone 12 hours with no loose movement; after a day without symptoms, other foods are added. Milk, fruit juices, rare meat, and soft eggs should not be given until recovery is complete.

The use of antibacterial drugs (sulfonamides, penicillin, or streptomycin) or of specific drugs for amebas or schistosomes may be begun at once in the presence of epidemics or of strong presumptive evidence for a specific etiology. As a rule it is advisable to defer such treatment in sporadic cases of diarrhea until the specific etiology is proved. Opium and its derivatives, castor oil and saline purges, and inert powders such as bismuth and kaolin, have been much used in diarrhea. They are needed rarely when physiologic therapy is applied, and merely diminish the discomfort when used without physiologic therapy in self-limited attacks. They are useless or even harmful in severe infectious diarrheas. In these, immediate proctoscopy and study of material obtained through the proctoscope reduces to a minimum the time needed for establishing the exact etiology, or at least for ruling out infections for which there is no specific treatment.

**Chronic Diarrhea.** This type of diarrhea may be due to ulcerative colitis or to regional inflammation of the lower ileum, cecum, colon, or rectum; it may be due to cancer or lymphosarcoma. Inflammation and stenosis near the anus often are due to lymphogranuloma; elsewhere, they may be due to amebas, tuberculosis, or non-specific disease. It may be a sequel of severe damage from acute colitis, with loss of mucosa and with submucosal granuloma formation. In all of these cases, blood and mucus occur with the small, frequent movements, and, in all, there is likely to be fever and a high sedimentation rate. The patient may still be able to do heavy work, or may be prostrated with high fever and anemia.

Low levels of serum albumin and edema of the legs often occur late in these conditions.

Emotional factors play a role in some cases in precipitating and aggravating ulcerative colitis, but it is noteworthy that the disorder occurs abruptly in patients who have not previously had mucus in the stools, or nervous diarrhea. Presumably, simple nervous indigestion, with large amounts of mouth flora and food reaching the ileum, permits the acute disorder to develop, or causes a flare-up. It also permits severe reactions to undigested food protein to which the patient may have become sensitized.

Uremia, amyloid disease, and leukemias may also lead to ulcerative bowel lesions and diarrhea.

Chronic abdominal distress and diarrhea with bulky, foamy, foul-smelling movements are the common manifestations of malabsorption of nutrient in the jejunum. This may result from cystic disease of the pancreas in infancy, or from pancreatitis, but as a rule, even when bile and pancreatic juice both are blocked by a lesion at the ampulla of Vater, diarrhea is entirely absent, or the bowel movements, free of bile and rich in neutral fat, are only slightly more frequent and bulky than normal. Achylia gastrica rarely causes diarrhea, and when it does, the stools are merely watery. With gastrocolic fistulas the unchanged food particles may be passed an hour or less after ingestion. The presence of undigested food particles in the stools, therefore, suggests marked hypermotility, deficiency of digestive enzymes, or gastrocolic fistula.

The usual cause of fermentative diarrhea is not failure of the proteins and fats to be split, but impaired jejunal absorption. In some cases this seems to be a functional defect in the villi, which remain hyperemic and swollen at all times and produce a curious roentgen pattern. In other patients the lacteals and mesenteric lymphatics are blocked by fatty acid crystals and by fat-laden macrophages. This disorder (Whipple's lipodystrophy) may not cause fatty diarrhea; it usually causes rapid wasting and death, after a relatively brief course. In still other cases, regional ileitis and jejunitis are demonstrable, and the lumen of much of the small bowel may be greatly narrowed and distorted. A few cases have been reported in which lymphosarcoma of the jejunum caused fatty diarrhea and the clinical picture of sprue.

Sprue, with sore mouth, diarrhea, and anemia, is seen very rarely in those who have not been in

the Orient or in tropical or semitropical climates, but macrocytic anemia and fermentative diarrhea may occur from nutritional deficiency in people who have never left the temperate zone in America, and may respond, as does sprue, to liver extract or folic acid. In all these types of steatorrhea, osteomalacia or osteoporosis, and low serum calcium, as well as signs of vitamin A deficiency, are likely to develop. In all, the serum albumin levels may be low. Formerly, chemical and microscopic analysis of the stools was relied on for the diagnosis. This is still helpful, but the roentgen study of the stomach and bowel, the trial of liver extract or of folic acid, and the test of the duodenal juice for lipase are the most essential data for diagnosis in this type of chronic diarrhea.

In all cases of bowel disease, proctoscopy and sigmoidoscopy are as much a part of the physical examination as is inspection of the mouth and pharynx in a patient with sore throat. Yet it is not a simple, painless, safe procedure. Proper preparation of the patient is needed in patients without diarrhea. Rupture of the rectum, with rapidly fatal peritonitis, has occurred even when experienced men were conducting the examination. X-ray of the abdomen for free gas should be made at once if there is the slightest symptom of damage at or after proctoscopy. To the experienced examiner the appearance is almost diagnostic in amebic dysentery, in bacillary dysentery, and in ulcerative colitis, and the material obtained from the ulcers is the best source for identifying pathogens by smear or culture. In the chronic diarrhea due to malabsorption of food, the rectum may be normal, or merely redder than normal; it rarely shows even small localized ulcers.

In addition to proctoscopy, the study of smears and cultures, x-rays of the lower ileum and colon, as well as a careful history, are essential. The response to the rice-and-applesause regime, and the effects of adding other foods, may suffice to establish food sensitivity as a factor in ulcerative colitis; specific therapy for pathogens may prove curative, and emetine may be tried, even though no amebas are found in cases resistant to other forms of treatment.

From the foregoing considerations, it is clear that in cases of constipation or diarrhea, the age of the patient, the duration of the symptoms, and the general state of health provide important

clues to the cause. When constipation has endured for many years, it is usually due to habit rather than to disease. Similar causes or systemic diseases are usually responsible in young adults. The onset of constipation after middle life in an elderly subject should immediately raise the suspicion of organic disease of the bowel (such as carcinoma), especially if the disorder is progressive. Diarrhea of brief duration is commonly due to dietary indiscretion, food intolerance, or infection by organisms of the *Salmonella* group. Prolonged diarrhea should lead to suspicion of infection (amebic or bacillary dysentery, tuberculous enteritis), of dietary deficiency (pellagra, sprue),

or of such intractable disorders as idiopathic ulcerative colitis and regional enteritis. Even when the complaint appears trivial, digital and instrumental examination of the rectum may yield important information. The significance of emotional disturbances, as either primary or aggravating factors in the causation of diarrhea and constipation, merits special emphasis.

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# 17

## Hematemesis and Melena

William H. Resnik

### Causes of Hematemesis and Melena

- Peptic Ulcer
- Carcinoma of the Stomach
- Portal Hypertension
- Miscellaneous Causes
- Procedure

Hematemesis (vomiting of gross blood) and melena (passage of tarry stools) are, with rare exceptions, manifestations of hemorrhage in the upper digestive tract: esophagus, stomach, duodenum. In this discussion hematemesis alone may be used for the sake of brevity, although it is to be understood that both symptoms may occur as a result of the same hemorrhage, or either may appear alone. Whether hematemesis or melena takes place will depend on whether vomiting is aroused when the stomach contains gross blood and on how much blood gains access to the small intestine. It has been demonstrated experimentally that at least 50 to 60 ml. of blood are necessary to give the stool a tarry appearance.

There are no clinical criteria that reveal accurately the size of the hemorrhage immediately after the event takes place. The statement of the patient regarding the amount of blood vomited is usually unreliable and, in any case, a variable

amount of blood has passed into the intestine. Blood counts and hematocrit determinations made shortly after the hemorrhage are of little value. After a number of hours have elapsed, when time has been allowed for compensatory restoration of plasma volume, the estimation of hemoglobin and hematocrit levels, frequently repeated, affords more accurate information regarding the extent of the blood loss, and may indicate whether bleeding is continuous or repeated. The severity of shock depends not only on the magnitude of the hemorrhage but also on the abruptness with which it takes place. Hemorrhage into the upper digestive tract is frequently associated with an elevation of the nonprotein nitrogen content of the blood, due primarily to absorption of the digestion products of blood, and enhanced in cases of extensive hemorrhage by the depression of renal function resulting from shock. The increase in the urea nitrogen content of the blood usually reaches a peak in about 24 hours following a single hemorrhage, and its level serves as a fair measure of the severity of the hemorrhage. Thus a normal figure denotes a favorable outcome; a figure of 70 to 100 mg. per

100 ml. of blood indicates a very large hemorrhage and, therefore, an unfavorable outlook. Elevation of temperature to 102° to 103° F., usually proportional to the size of the hemorrhage, is manifest within 24 hours of the onset of bleeding and may last several days; the cause is uncertain.

### CAUSES OF HEMATEMESIS AND MELENA

**Peptic ulcer** is the most common cause of hematemesis, constituting 40 to 80 per cent of the cases in different series. Hemorrhage from duodenal ulcer comprises about 75 per cent of all bleeding ulcer cases. In most instances there is a history characteristic of ulcer or the ulcer has been demonstrated by x-ray study. In a small percentage hematemesis or melena may be the initial symptom. Bleeding usually results from the rupture of a small vessel in the ulcer or from an adjacent area of gastritis. More uncommonly, bleeding follows the erosion of a large sclerotic artery; it is in these latter cases that fatal hemorrhage is likely to ensue.

**Carcinoma of the stomach** accounts for about 5 per cent of the cases of hematemesis. Although ordinarily considered to be a rather uncommon cause of profuse hemorrhage, the incidence in one large series of massive hematemeses was 19 per cent.

**Portal hypertension** is responsible for about 5 to 10 per cent of the cases, bleeding being due to rupture of an esophageal varix. Of this group, cirrhosis of the liver (usually the Laennec type, and in certain regions liver disease due to schistosomiasis) is the most frequent cause. In the remainder, congestive splenomegaly without cirrhosis (splenic anemia or Banti's syndrome) is found.

**Miscellaneous Causes.** In the miscellaneous group fall the rarer causes of hematemesis and melena: uncommon tumors of the stomach, duodenum, and small intestine; hiatus hernia; the various blood dyscrasias, etc.—about 2 to 3 per cent of the total.

Ordinarily, x-ray and other examinations are not instituted until two or three weeks have elapsed after the bleeding has subsided. At this time careful study fails to reveal any adequate cause for the hemorrhage in a considerable number of cases, varying in different reports from 3

to 25 per cent. In some, a typical history of ulcer makes it probable that the ulcer has healed before the diagnostic studies were carried out. In others, subsequent observations will disclose a lesion, not presently discernible, that was the probable cause of the hemorrhage. In still others, depending on the frequency with which gastroscopic examination has been employed, gastritis will be discovered to have been the probable basis of the bleeding. In the remainder, it must be assumed that hemorrhage was the result of bleeding from a superficial ulcer or erosion in the stomach or duodenum.

Hematemesis and melena may be due to a large number of disorders. However, the problem of diagnosis is simplified if it is borne in mind that 90 per cent of all cases are due to primary intragastric diseases: peptic ulcer (including duodenal and gastrojejunal ulcers), cancer of the stomach, and superficial ulcerations and erosions of the stomach and duodenum. Most of the remainder are due to bleeding from esophageal varices.

### PROCEDURE

The first obligation is to combat shock resulting from the loss of blood volume, and then to exclude hemoptysis and bleeding from the nose and pharynx as possible sources of swallowed blood. During the first few days when these measures are being instituted, historical data regarding indigestion, alcoholism, previous episodes of bleeding from the stomach or elsewhere, and physical findings such as a palpable suprACLAVICULAR lymph node, jaundice, enlargement of the liver and spleen, spider angiomas, may lead to a definite or probable diagnosis of the underlying disorder. During this time hematologic studies may also be pursued if there is suspicion that a blood dyscrasia is present. Roentgenographic investigation may be undertaken as soon as evidences of gross bleeding have disappeared, provided the examination is made cautiously and with due regard for the possibility that bleeding may recur. In cases of less urgency, this examination is usually deferred until two to three weeks after the bleeding has subsided, and then careful attention should be directed to the lower end of the esophagus for the presence of varices and to the small intestine below the duodenal cap for lesions that might otherwise be overlooked. If the

diagnosis continues to remain in doubt, gastroscopic examination, gastric analysis, and liver function tests are then made.

It is not to be inferred that all patients who have had hematemesis will necessarily be treated medically, according to the plan outlined above. Although the indications for surgical intervention are not yet clearly established to the satisfaction of all students of the problem, this type of treatment may be employed in some instances.

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# 18

## Jaundice and Disorders of Liver Function

M. M. Wintrobe

### Definition

Normal Manner of Blood Destruction

### Contents of Bile

### Functions of the Liver, Liver Function Tests

Tests Concerned with Excretion of Bile Pigments

Tests Concerned with Excretion of Other Waste Products, Toxic Substances, or Abnormal Substances Artificially Introduced

Tests Related to Protein Metabolism

Tests Dealing with Carbohydrate Metabolism

Tests Related to Fat Metabolism

Miscellaneous Tests of Hepatic Function

### Various Forms of Jaundice

### Study of a Case of Liver Disease

### DEFINITION

Jaundice refers to a state in which the patient's scleras and skin, and to some extent even the mucous membranes, assume a greenish yellow hue as the result of staining by bile pigment. The intensity of jaundice varies greatly, ranging from a barely perceptible discoloration of the scleras with no evident change in the skin, to a very deep pigmentation of both scleras and skin in which the former are intensely yellow and the latter becomes almost brown in hue. Jaundice is visible in the mucosa of the hard palate or in the lips when compressed with a glass slide. Jaundice is easily overlooked in Negroes. The term "latent" jaundice is sometimes used to refer to a degree of bilirubinemia which is so slight that no change is noticeable in the skin, and the scleras are normal in appearance or only questionably

tinged. The abnormal state in such cases is detectable with certainty only by laboratory means.

The bile pigments are derived from the red blood corpuscles. An increase above the normal in the bile pigments of the plasma occurs when red corpuscle destruction is greater than normal, or when liver function is impaired; also, since the liver modifies the bile pigments and excretes them, jaundice develops when there is obstruction of the bile passages. When the concentration of bile pigment in the blood plasma exceeds 2 mg. %, jaundice will usually be observed.

The interpretation of jaundice requires a knowledge of the normal manner of blood destruction and an understanding of liver function, as well as of the various tests employed in the measurement of these functions, including means whereby the patency of the bile passages can be determined.

### NORMAL MANNER OF BLOOD DESTRUCTION

Under normal conditions, as the result of the wear and tear entailed in the passage of the red blood corpuscles through the circulation, about  $\frac{1}{120}$  of all the red corpuscles in the body are broken down each day; that is, the "life" of the average red corpuscle is thought to be about 120 days. The exact mode of destruction of the red cor-

puscles is not known, but it appears that they are broken down by the cells of the reticuloendothelial system. These cells are found chiefly in the liver, spleen, and bone marrow, but they are present also in the subcutaneous tissues and are widely scattered throughout the body. It is through the action of these cells that a contusion or hemorrhage under the skin can be seen to

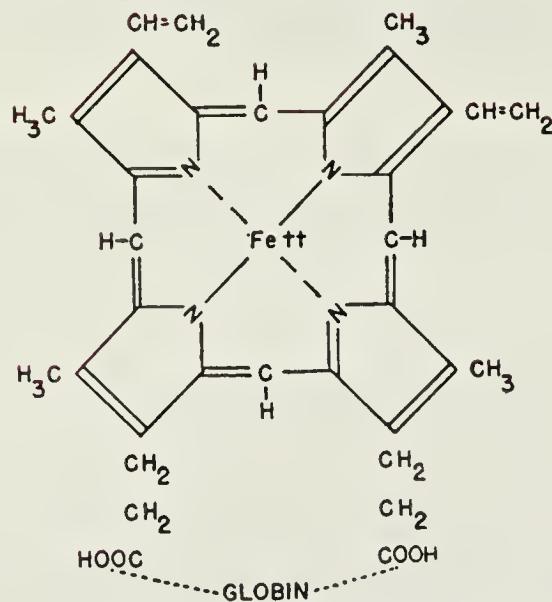


FIG. 29. Chemical structure of hemoglobin, showing one molecule of heme (iron joined to the porphyrin nucleus) attached to globin. Hemoglobin is actually composed of four molecules of heme bound to one molecule of globin. (Courtesy, Wintrobe: "Clinical Hematology," 2d ed., Philadelphia, Lea & Febiger.)

change in color from a dark blue to brown, green, and then yellow, these changes occurring as the red cells are fragmented and the products of their destruction are gradually removed. The liver disposes of the bilirubin released by the reticuloendothelial system. It is the failure of this function through hepatic disease or biliary obstruction, or because of inability of the liver to cope with the increased amounts of bile pigment brought to it, which leads to the development of jaundice.

**X** Hemoglobin forms approximately 90 per cent of the red corpuscle (dry weight). As indicated in figure 29, hemoglobin consists of porphyrin, iron, and globin. The porphyrin has been designated protoporphyrin 9, type III. Like other porphyrin rings, it consists of four pyrrole nuclei connected to one another by methine ( $-\text{CH}=$ ) bridges. The porphyrin-iron complex is known as heme. Four of these heme molecules are joined to one molecule of globin.

It is now generally believed, although it has not yet been proved conclusively, that hemoglobin is first broken down by the opening of the  $\alpha$  methine bridge in the porphyrin nucleus, the iron remaining and the union with globin persisting to form a green bile pigment-iron-protein compound known as *verdohemoglobin*. Iron is then split off and travels henceforth with the globin

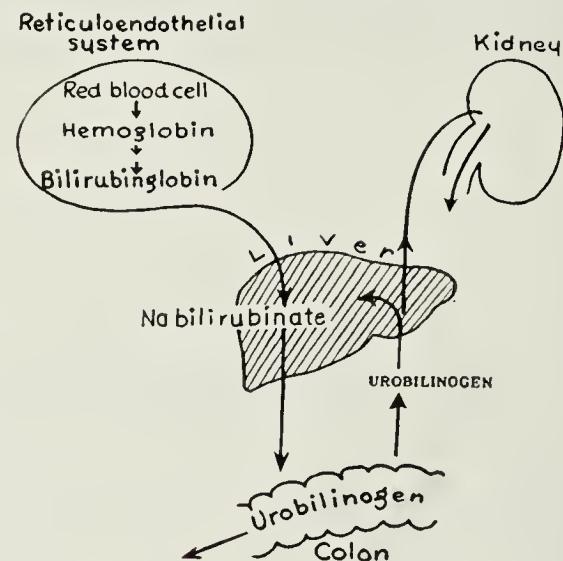


FIG. 30. Diagram of steps leading from destruction of red corpuscles to excretion of urobilinogen in normal subjects. (Courtesy, Young: *New England J. Med.*, 237:225, 1947.)

fraction of the plasma as "plasma iron." The globin probably remains attached for a time to the remainder of the hemoglobin—namely, bilirubin—in which form it is carried in the plasma albumin fraction. It is in this form ("bilirubin-globin") that bilirubin is presented to the liver where, through the activity of the Kupffer or the parenchymal liver cells, the globin is detached and returned to the body pool of protein. The bilirubin, now freed of iron and of globin, is a waste product (fig. 30). This passes into the bile canaliculi and thence through the bile ducts, including the common bile duct, to the duodenum.

The further course of bilirubin is of interest, since in pathologic states, and to some extent in the normal individual, certain derivatives seem to be reabsorbed from the bowel. Through the activity of the bacterial flora of the intestines, bilirubin is reduced and converted in the colon to mesobilirubinogen, a colorless compound giving the Ehrlich reaction. On exposure to light and air, this substance develops urobilin characteristics and becomes orange-yellow in color. The Ehrlich reaction gradually disappears. This transition can be hastened by a mild oxidizing agent

such as iodine, a characteristic which forms the basis of the Schlesinger (alcoholic zinc acetate) qualitative test for urobilin.

Actually mesobilirubinogen is not the sole urobilinogen. Stercobilinogen is another substance giving the Ehrlich aldehyde reaction for urobilinogen. *d*-Urobilin and urobilin IX,  $\alpha$ , are derived from this or possibly from other chromogens. As far as present knowledge goes, however, the clinical significance of all of these substances is the same. The quantitative determination of urobilinogen in urine or stools fortunately includes all the chromogens which have been mentioned.

Although some investigators still maintain that the urobilinogens in the urine come directly from bilirubin in the plasma, it is generally held that the urobilinogens in the urine are derived from pigments which are absorbed from the bowel into the portal circulation, and are returned to the liver. In any event, it is well established that the liver normally clears the blood of urobilinogen and passes it on to the gut. In the presence of liver injury or lowered function of the liver cells, varying fractions of the urobilinogen are refused and go over into the general circulation to appear in the urine; increased amounts of urobilinogen are also found in the urine as well as in the stool when blood destruction is increased. It is important to bear in mind that, when bilirubin is prevented from entering the intestines, urobilinogen will not be formed, and hence will not be found in more than traces in either feces or urine. Thus, in jaundice due to unremitting obstruction (as is usually the case with tumors), little or no urobilinogen is found in the urine or stool. In jaundice due to intermittent obstruction, as is often the case with stone, is associated with marked fluctuations in urobilinogen in the urine and stool. In the presence of liver injury or lowered hepatic function, the quantity of urobilinogen in the urine is increased; this is also the case when bilirubin is formed in excess (hemolytic anemias), in which event increased amounts are found in the stool as well.

#### CONTENTS OF BILE

When jaundice is observed, it must be kept in mind that, if it is due to obstruction to the flow of bile, a number of substances in addition to bile pigments are retained. These include the bile salts, cholesterol and cholesterol esters, fatty

acids, phospholipids, inorganic constituents of the blood plasma, and certain enzymes such as phosphatase. Complete information concerning the composition of bile is still to be obtained. The bile salts are toxic and the retention of still other constituents of bile may also have ill effects. Furthermore, the lack of bile in the intestines deprives the organism of the normal role of this secretion. It is the function of the bile to augment intestinal motility, facilitate the digestion and absorption of fat, and aid in the absorption of fat-soluble substances such as vitamins A, D, and K, as well as of calcium and iron. Bile also buffers the acid chyme from the stomach and exerts a bacteriostatic action on the feces. The bile salts, furthermore, are important in keeping the fatty acids in aqueous solution at the acid reaction of the gallbladder, thus preventing the precipitation of cholesterol and fatty acids there.

#### FUNCTIONS OF THE LIVER. LIVER FUNCTION TESTS

The symptoms and signs of hepatic insufficiency, other than jaundice, are often vague, and correspond to those of many systemic diseases.

The symptoms of latent liver disease often resemble those of chronic exhaustive states. There may be anorexia, nausea, and vague abdominal pain. Physical activity may aggravate the ill-defined complaints and an incorrect diagnosis of neurasthenia or of psychoneurosis may be made. Even when jaundice has attracted attention to the liver, subsidence of this sign is not necessarily correlated with repair of liver damage.

For the purpose of detecting the presence of liver disease and determining its extent, as well as for the differentiation of the various types of jaundice, it is necessary to understand the functions of the liver and the methods available for their appraisal. The functions of the liver include:

1. Those concerned with the excretion of bile pigments.
2. Those concerned with the excretion of other waste products, toxic substances, or abnormal substances artificially introduced.
3. Those related to protein metabolism.
4. Those dealing with carbohydrate metabolism.
5. Those related to fat metabolism.
6. Miscellaneous functions.

When the multiplicity of functions of the liver is considered, it is not surprising to find that

there is no simple index or test to gauge the competency of this organ. It is important to observe that reduction in hepatic efficiency is not symmetric, one or more important functions sometimes being impaired when others remain normal. Furthermore, there is a large hepatic reserve which permits destruction of a major fraction of the cells without evidence of insufficiency. Thus urea formation and blood sugar regulation, even though very important functions of the liver, become impaired only in the most extreme phase of liver dysfunction. Nevertheless, if a disorder affects all the cells, minor damage may be detected. Functional insufficiency is not directly correlated with demonstrable histologic changes; indeed, it may exist in their absence. Likewise, clinical symptoms may be encountered when laboratory evidences of dysfunction have cleared, whereas symptoms may be insignificant even though extensive hepatic disease exists. The size of a liver is no index of its functional capacity, although a liver greatly reduced in size is more likely to be impaired than one which is excessively large.

There are several types of hepatic functional failure. The defect may involve the parenchymal cell; it may be vascular, limiting portal or arterial flow, or it may interfere with biliary drainage. Not infrequently these three types of failure co-exist in varying degree or may follow one another. Thus prolonged disease of the parenchymal cells with the resulting change in architecture is usually followed by vascular failure.

#### TESTS CONCERNED WITH EXCRETION OF BILE PIGMENTS

These include the icterus index test, the van den Bergh test, the bilirubin excretion or tolerance test, and the examination of the urine and feces for bilirubin and the urobilinogens.

**Icterus Index.** The icterus index (Meulen-gracht) test is a nonspecific procedure whereby the color of the blood plasma is matched against standards of potassium dichromate. More precise measurements can be made with a photoelectric colorimeter. This test simply indicates the degree of yellowish discoloration of the plasma. Since this is most often due to accumulation of bilirubin, it has proved to be a useful even though a rough guide for the detection and measurement of jaundice. It must be remembered that other pigments, particularly carotene, may pro-

duce the same discoloration. A more specific measure is found in the van den Bergh test.

**Van den Bergh Test.** This measures bilirubin specifically and distinguishes various forms of bilirubin; namely, "free" bilirubin and "bilirubinglobin." Consequently, the test is of considerable value in aiding the differentiation of various types of jaundice. The test is based on Ehrlich's discovery that a mixture of sulfanilic acid, hydrochloric acid, and sodium nitrite (diazo reagent) yields a reddish violet color when added to solutions containing bilirubin, such as blood plasma. The color may appear and reach its maximum intensity at once (prompt, *direct*, or "one-minute" reaction). If no color develops in one minute, alcohol is added; if the reddish color now appears, the reaction is called *indirect*. The addition of alcohol is believed to release bilirubin from the union with protein. Actually, it seems that both direct and indirect types of bilirubin are associated with the serum albumin. However, the "indirect" bilirubin may be bound with valence bonds to globin, which has a mobility similar to that of albumin in electrophoretic determinations, whereas the prompt, "direct" reacting type seems to be adsorbed loosely by the serum albumin. There may also be chemical differences in the bilirubin molecule involved in these two types of reaction. In any event, as the bilirubinglobin in the plasma passes from the liver sinusoids to the bile canaliculi it is divested of its protein. The free bilirubin exhibits a prompt, direct ("one-minute") reaction. When this type of bilirubin returns to the blood because of regurgitation of bile as the result either of increased intrabiliary pressure or of bile capillary injury, it becomes loosely adsorbed on the serum albumin, but in this state it is still capable of giving a prompt, direct van den Bergh reaction. When the blood plasma contains free bilirubin as well as bilirubinglobin in increased amounts, as is found, for example, when severe parenchymatous liver disease is present, a *biphasic* reaction is obtained.

Normally, 0.5 to 0.8 mg. of bilirubin is found per 100 ml. of blood. The "one-minute" bilirubin is less than 0.2 mg. in normal persons, and thus the normal quantity of "indirect" bilirubin  $(T - 1')$  is 0.3 to 0.6 mg. The amount of urobilinogen excreted in the urine of the normal adult in 24 hours (U.U.) is 0 to 3.5 mg., most frequently 0.5 to 1.5 mg. If a simpler semiquanti-

tative procedure is used, such as the two-hour afternoon sample of urine, the normal value for urinary urobilinogen is not greater than one "Ehrlich unit." (This is an arbitrary color unit with no established value in milligrams.) The random sample of feces should not normally contain more than 400 Ehrlich units of urobilinogen per 100 Gm. The normal range for the feces urobilinogen (F.U.), as calculated from a four-day period of collection, is 40 to 280 mg. per day, usually 100 to 200 mg.

**Bilirubin Tolerance Test.** Since the liver possesses substantial reserve capacity, the retention of bile pigments, as indicated by the van den Bergh reaction, is not so sensitive a measure of liver function as is obtained by overloading the liver through the intravenous injection of a measured amount of bilirubin. This is the principle of the *bilirubin tolerance test*. The rapidity with which the bilirubin is cleared from the blood plasma is measured. Retention in excess of 5 per cent after four hours is regarded as evidence of impaired liver function. It is to be noted that this test is without meaning as to the function of the liver if hyperbilirubinemia is present.

**Harrison Spot Test.** The presence of bilirubin in the urine is detected most simply by the *Harrison test*, which depends on the reaction of bilirubin with barium chloride and the Fouchet reagent. This test has been modified to offer a very simple semiquantitative estimation by using filter paper impregnated with barium chloride. A Harrison "spot reaction" of one plus or greater is regarded as positive. Somewhat less sensitive, and not specific, is the *methylene blue test* (Franke).

### TESTS CONCERNED WITH EXCRETION OF OTHER WASTE PRODUCTS, TOXIC SUBSTANCES, OR ABNORMAL SUBSTANCES ARTIFICIALLY INTRODUCED

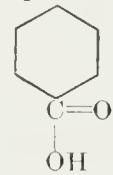
**Bromsulfalein Test.** The most useful of the tests classifiable under this heading is that in which a dye, *bromsulfalein*, is injected and its removal from the blood measured. When 5 mg. per kilogram body weight is injected, intravenously, none, or at most no more than 5 per cent, should remain in the blood stream after 45 minutes. As in the case of the bilirubin tolerance test, the bromsulfalein test gives no indication of

liver function if there is obstruction of the bile ducts, since this alone will cause a prolonged retention of dye in the blood plasma. Likewise, in instances of very extensive destruction of the liver parenchyma where the continuity of the bile ducts is broken, as in acute yellow atrophy and in severe toxic jaundice, falsely high values may be found. In such cases the abnormal retention of the dye need not be an expression of failure of the liver cells to excrete it, since the obstruction of the intrahepatic bile channels as a result of their lack of continuity will cause the retention of the dye in the blood stream.

Recent studies of the excretion of bromsulfalein indicate that, when the dye is introduced into the circulation by prolonged intravenous infusion, its rate of removal attains a maximum which is independent of the plasma concentration. Thus a function similar to a "Tm" of the kidneys is obtained. The value of this maximum rate (= "Lm" [bromsulfalein]) should, by analogy, be proportional to the functional hepatic mass in respect to transfer of the dye, thus affording quantitation of a hepatic capacity. Since the procedure involves a maximum load, it is possible that it may be found to represent a more sensitive quantitative evaluation of liver function than the previously available tests. The principle involved may be applicable to a number of hepatic functions.

**Hippuric Acid Test.** When benzoic acid enters the body it is, in the main, combined with glycine to form hippuric acid; a fraction of the benzoate is conjugated with glucuronic acid and excreted in the urine. Quick's hippuric acid test is a measure of the capacity of the liver to synthesize glycine, and also of the enzymatic mechanism (present also in small part in the kidneys) which

unites benzoic acid



with aminoacetic

acid (glycine). After oral ingestion of 6 Gm. of sodium benzoate, the urine is collected four hours later, and its content of hippuric acid measured. Normally, the output of hippuric acid is from 3 to 3.5 Gm. during a four-hour period. Factors influencing the result are the rate and completeness of absorption, as well as the ability of the kidney to excrete the hippuric acid formed. The latter can be judged by performing, simultaneously, a phenolsulfonphthalein renal function test. To

eliminate the factor of absorption from the gastrointestinal tract, an intravenous test has been devised. In this procedure 1.77 Gm. of sodium benzoate dissolved in 20 ml. of water is injected, and the urine is collected an hour later. The normal output of hippuric acid is 1 Gm. (0.7 Gm. of benzoic acid).

The hippuric acid test gives some indication of the degree of damage of the liver but does not differentiate extrahepatic and intrahepatic jaundice, for, when obstruction is of long standing, secondary hepatic damage is apt to occur. Since benzoic acid, as already mentioned, is normally conjugated with glucuronic acid, the excretion of glucuronate following the ingestion of benzoic acid has been proposed as a measure of hepatic function, and is claimed to be more sensitive than the hippuric acid test.

#### TESTS RELATED TO PROTEIN METABOLISM

The liver is intimately concerned with the maintenance of normal plasma proteins. The diseased liver is unable to produce albumin as readily as the normal liver, and the more severe the hepatic insufficiency the greater the impairment of this function. The serum globulin, on the other hand, may be increased in amount. Electrophoretic analysis as well as newer chemical techniques have revealed, furthermore, that the distribution of the serum globulin fraction may be definitely abnormal in spite of a normal albumin-globulin ratio as determined by the sodium sulfate (Howe) method. Electrophoretic studies indicate that a large increase in the gamma-globulin fraction with a decrease in the serum albumin is the most characteristic abnormality of the serum proteins in liver disease. Significant increases in beta-globulin also are observed in all types of liver disease. Although very severe liver disease is associated with a reduction in plasma fibrinogen, in most instances of hepatic dysfunction the fibrinogen level is raised.

In cirrhosis of the liver with severe diffuse hepatic damage of long standing, the protein abnormalities are more pronounced than in any other form of liver disease. An increase in serum globulin, with inversion of the albumin-globulin ratio, is a common finding. It is of interest that the least pronounced gamma-globulin abnormalities have been observed in cancer of the liver.

Normal gamma-globulin values have been found in extrahepatic jaundice.

Several tests of liver function which are now in common use depend, in all probability, on alterations in plasma protein constituents consequent to altered liver functions, but different types of alterations may be responsible for abnormal findings in the various tests. These function tests include the cephalin-cholesterol flocculation test, the thymol turbidity and flocculation tests, the colloidal gold test, and the Takata-Ara reaction.

**Cephalin-Cholesterol Test.** The cephalin-cholesterol test of Hanger is a flocculation reaction which is usually positive in diseases characterized by diffuse inflammation of the liver parenchyma. An emulsion of cephalin and cholesterol, carefully prepared and standardized, is added to diluted serum and the degree of flocculation and precipitation is noted after 24 and 48 hours. The serums of normal subjects give a negative test. Likewise, the serums of patients with disease of the bile ducts or chronic passive congestion of the liver usually give negative tests, whereas in cases of hepatitis positive reactions are found during the active stage of the disease. A moderately positive reaction may be observed also when there is acute degeneration in the liver. In conditions characterized by high serum globulin, such as sarcoid and lymphogranuloma venereum, false positive reactions may be observed.

It has been shown that the electrophoretically separated albumin fraction of normal serums, if present in sufficient concentration, tends to inhibit the flocculation produced by the gamma-globulin fraction, whereas albumin fractions from the serums of patients with hepatitis produce relatively less inhibition of the flocculation. Isolated gamma-globulin fractions obtained from normal serum, and from the serum of cases of hepatitis, cause flocculation of a cephalin-cholesterol emulsion. Thus the increase of gamma-globulin which is associated with liver disease, and the diminution of serum albumin, as well as a diminution in the flocculation-inhibiting properties of the albumin fraction, appear to be the factors leading to the changes which are demonstrated by the cephalin-cholesterol flocculation test.

**Thymol Turbidity Test.** The thymol turbidity test of Maclagan depends on the reaction of various human serums with a buffered thymol solution. Serum lipids and lipoprotein complexes mi-

grating electrophoretically in the beta-globulin fraction play an essential role in the reaction. The degree of elevation of the gamma-globulin fraction is also important. This test offers an advantage over the Hanger test in that it depends on the use of an easily prepared stable solution containing specific amounts of pure chemicals. Furthermore, the test can be completed in  $\frac{1}{2}$  hour instead of 48 hours. The result is measured in units; in the normal, the value obtained does not exceed 4 or 5 units. In disease, values as high as 24 and even 40 units may be observed.

It has been pointed out that this is not a liver function test in the true sense of the word. In contrast to the bilirubin content of the plasma, the thymol turbidity has shown no correlation with the severity of symptoms in cases of infectious hepatitis. Yet it is a very sensitive indicator of acute liver damage. It is likely that the underlying mechanisms of the cephalin-cholesterol flocculation and the thymol turbidity tests are not identical, even though their results are often parallel.

**Colloidal Gold Test.** This test appears to depend on the detection of increased amounts of globulin in the serum by precipitation with gold. The addition of pure gamma-globulin to normal blood serum produces a positive serum colloidal gold reaction. The *Takata-Ara reaction* depends on similar but probably not identical factors. Each of these tests related to protein substances probably is a measure of a different complex of factors.

#### TESTS DEALING WITH CARBOHYDRATE METABOLISM

Much less sensitive as a measure of diffuse liver disease than the procedures which have been mentioned already, and more cumbersome to carry out, are liver function tests related to carbohydrate metabolism. Of the sugars, the utilization of galactose, taken orally or injected intravenously, has been used as the preferred test, since its metabolism appears to be more nearly limited to the liver. The utilization of sodium *d-lactate* has also been introduced as a measure of liver function, since this substance represents an intermediate stage in carbohydrate metabolism in the cycle involving striated muscle and liver. Because these tests can be performed under circumstances when simpler procedures like the bromsulfalein test cannot be applied, as in ob-

structive or regurgitation jaundice, and because their comparative insensitivity results in normal reactions when only a mild degree of hepatic functional impairment is associated with biliary obstruction, the chief field of usefulness of the galactose tolerance test and the *d-lactate* test is in aiding the differentiation between obstructive and nonobstructive jaundice. Even in this connection, however, their application is limited.

#### TESTS RELATED TO FAT METABOLISM

The liver probably synthesizes cholesterol esters and maintains a constant ratio between free cholesterol and cholesterol esters in the blood. The total cholesterol in normal human plasma varies, in the majority of persons, between 150 and 250 mg. % (the extremes are 107 and 320 mg. %), with the ester fraction ranging between 68 and 76 per cent of this total. The most frequent disorder of serum lipids in liver disease is an increase in the ratio of free to total cholesterol. Free cholesterol usually is not only relatively but also absolutely increased. The cholesterol ester fraction, on the other hand, is reduced even to virtual complete disappearance when extreme damage exists.

In most patients with portal cirrhosis, the total cholesterol and lipid phosphorus have been found normal or subnormal, tending to fall as the disease advanced. It would appear that hypolipemia arises from extensive degeneration or destruction of liver parenchyma. Unfortunately, from the standpoint of the usefulness of this test in some varieties of toxic hepatitis, and in the regenerative phase of hepatitis, both the cholesterol and cholesterol ester content of the blood may be elevated.

Hyperlipemia may possibly be simply a product of biliary obstruction. The total cholesterol and lipid phosphorus have been found to be elevated in the serum when biliary obstruction existed. This may explain the increased amounts which have been observed in a certain proportion of patients with biliary cirrhosis and in some cases of infectious hepatitis, for in many of these cases intense jaundice had been present.

#### MISCELLANEOUS TESTS OF HEPATIC FUNCTION

**Alkaline Serum Phosphatase Level.** Phosphatase is an enzyme which originates in the bone-

producing cells. It enters the blood and passes through the liver to be excreted into the bile.

**The normal range** of alkaline serum phosphatase as measured by the Bodansky method is 1 to 4 units. When there is **biliary obstruction**, the alkaline phosphatase rises promptly in the blood to values greater than 10 units. In hepatitis there is usually but little increase. Measurement of alkaline serum phosphatase has been used, therefore, as an aid in distinguishing intra- and extrahepatic forms of jaundice. Unfortunately, overlapping occurs. It is to be noted, furthermore, that the alkaline serum phosphatase level is a nonspecific measure of liver function, since increases may occur in certain bone disorders.

**Response of Plasma Prothrombin to Injection of Vitamin K.** The liver is concerned in some way with the formation of prothrombin, and for this vitamin K is necessary. This vitamin, being fat-soluble, is not absorbed from the bowel unless bile is present. Consequently, either liver disease or biliary obstruction can be the cause of low plasma prothrombin levels. In the presence of severe liver disease, however, in contrast to what is found when biliary obstruction is the cause of the hypoprothrombinemia, the plasma prothrombin does not rise when vitamin K is administered parenterally. A measure of liver function, therefore, is the rise in prothrombin level following the intramuscular administration of vitamin K (2 mg. of menadione). When liver function is normal, the prothrombin will rise more than 20 per cent in 24 hours.

Table 12

TESTS RECOMMENDED FOR STUDY OF DISEASE OF THE LIVER

(In order of simplicity and usefulness)

In the Absence of Jaundice	In the Presence of Jaundice
Bromsulfalein excretion	Quantitative van den Bergh Urine bilirubin (Harrison test) Urine and stool urobilinogen Alkaline serum phosphatase Serum cholesterol and cholesterol esters Galactose tolerance
<i>In the Absence or Presence of Jaundice</i>	
Thymol turbidity Cephalin-cholesterol flocculation Serum albumin and A/G ratio Vitamin K test Hippuric acid test	

In addition to those listed above, there are many other less commonly used procedures for testing the function of the liver. It is evident that the testing of liver function is a complex procedure which requires an understanding of metabolism as well as of liver physiology. Furthermore, in applying liver function tests, discrimination must be used, for obviously all the tests can rarely be employed in a given case; nor are they all needed. Nevertheless, since the functions of the liver are so numerous, it is desirable in many instances to use a battery of procedures in attempting to assay the status of the liver (see table 12). A discussion of the liver function tests which are most likely to be useful in the various disorders of the liver must, however, be preceded by a consideration of the various types of jaundice.

### VARIOUS FORMS OF JAUNDICE

Jaundice has been classified as (1) obstructive; (2) parenchymatous, hepatocellular, toxic, or infectious; and (3) hemolytic. From the standpoint of pathogenesis, the types of jaundice may be distinguished as being due to either (1) retention of bile pigment or (2) regurgitation.

**Retention jaundice** represents hepatocellular inability to remove bilirubin from the circulating blood. This may be associated with an overproduction of bilirubin. The bile ducts are patent but the liver cells may show swelling, necrosis, or atrophy. Bilirubin-globin is retained but other bile constituents are not accumulated. The van den Bergh reaction is delayed or indirect in type; the "one-minute" ("direct") bilirubin is normal in amount. Bilirubin is not found in the urine, regardless of the degree of hyperbilirubinemia. Instead, increased amounts of urobilinogen are found in the stools and urine.

**In regurgitation jaundice** it is probable that whole bile is returned to the blood stream. The bilirubin which is returned to the blood has been freed of its close bond with globin, and the "one-minute" bilirubin is increased ("direct" or prompt van den Bergh reaction). The amount of fecal urobilinogen is decreased, and bilirubin and bile salts instead of urobilinogen are present in the urine. There may be no urobilinogen in the urine or only reduced amounts; at times there may be increased amounts, depending on the quantity of bile pigment reaching the intestines, for, as stated above, it is the urobilinogen which

is reabsorbed from the colon and subsequently refused by the liver which is excreted in the urine. The pathologic basis of regurgitation jaundice is increased intrabiliary pressure with rupture of the bile capillaries resulting from obstruction of the ducts or damage to these structures with increased permeability (fig. 31). The bile probably

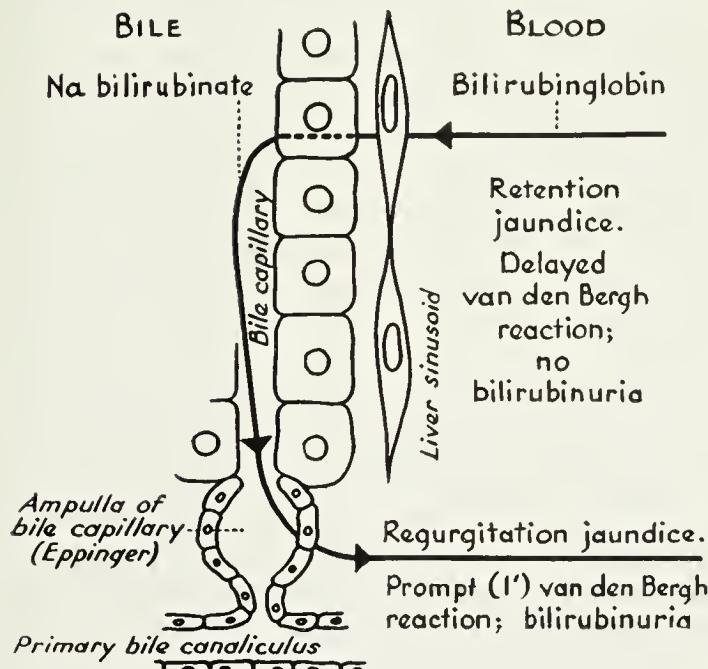


FIG. 31. A concept of the physiologic basis for the prompt and delayed van den Bergh reactions, as seen in retention and regurgitation jaundice, respectively. (Watson: *Blood*, 1:104, 1946; courtesy, Grune & Stratton).

gains access first to the lymph spaces of Dissé and thence to the thoracic duct and the blood.

The classification of jaundice just outlined has the drawback that those forms of jaundice due to biliary obstruction and those caused by parenchymal liver damage are grouped under one heading—namely regurgitation jaundice. It is of great practical importance to distinguish these two types of jaundice. A classification which is more complete and seems to be more practical and useful than those described hitherto is presented in table 13, where the corresponding terms of the earlier classifications are also listed.

In *prehepatic jaundice* there is no demonstrable lesion in the liver. This form of jaundice is usually due to *increased blood destruction*. Anemia, reticulocytosis, often spherocytosis, and splenomegaly are associated findings. Depending on whether or not the hemolytic anemia is chronic or acute and, in part, according to the nature of the underlying disorder, symptoms may be few or pronounced (weakness, dyspnea, chills, fever, back pain, vascular disturbances, etc.). In the acute forms, and in certain chronic types, leukocytosis is often present as well as a "shift to the left" in the myeloid series of leukocytes. In other cases there is leukopenia. Sometimes an increase in the number of platelets is also found. There is hyperbilirubinemia but the prompt or "one-minute" van den Bergh reaction is negative or relatively low.

Also "prehepatic" is a rare and benign form of jaundice which has been variously referred to as "*hereditary nonhemolytic bilirubinemia*," "*familial nonhemolytic jaundice*," or "*constitutional hepatic dysfunction*." This is associated with no symptoms or anemia and there is no evidence of increased blood destruction. The bilirubinemia is of the indirect-reacting type but there is neither bilirubinuria nor increased urobilinogenuria. Hepatic function tests give normal results and the liver is normal histologically.

*Hepatic jaundice* is that form which is attributable to injury or disease of the liver itself. Two types are distinguished: (1) Those cases in which the histologic examination reveals changes in the hepatic cells (*hepatocellular*); and (2) those in which the bile canaliculi are the site of the injury, the hepatic cells being relatively normal (*hepatocanalicular*).

Infectious and serum hepatitis are common causes of *hepatocellular jaundice*. Similar impairment in liver function and cell injury may also be produced by toxins (pneumococcal pneumonia, bacterial peritonitis, hemolytic streptococcus septicemia, gas-bacillus sepsis) and poisons (arsphen-

Table 13  
VARIOUS CLASSIFICATIONS OF JAUNDICE

Jaundice	Rich	McNee	Ducci
	Retention	Hemolytic	Prehepatie { Hemolytic
	Regurgitation	Toxic and infective	Nonhemolytic
		Obstructive	Hepatic { Hepatocellular
			{ Hepatoanalicular
			Posthepatie { Incomplete
			Complete

amine, cinchophen, phosphorus, trinitrotoluene, sulfanilamide). In chronic passive congestion, hepatic flow may be reduced and liver function impaired. Under such circumstances the added bilirubin production from pulmonary infarction may precipitate frank jaundice and signs corresponding to those of early hepatocellular jaundice. Cirrhosis, of whatever cause, when accompanied by jaundice, generally presents the features of the hepatocellular form of hepatic jaundice.

The symptoms and signs differ to some extent in accordance with the cause of the jaundice, and depend in part on the stage of the condition. Thus ~~infectious hepatitis~~ often begins with anorexia, lassitude, fatigue, nausea, and vomiting, and at this stage bile may be demonstrated in the urine even before the serum bilirubin exceeds 1 mg. As the process advances, the urine becomes frankly dark and the stools become acholic. If acholia develops, however, it seldom lasts over seven days, a useful point in differentiating hepatocanalicular and posthepatitis types of jaundice. Low values for fecal urobilinogen are found during the acute phase, and a gradual increase occurs, even to values above normal, during recovery. It is noteworthy that simple inspection of the stools may be misleading, as grossly acholic feces may contain from 10 to 15 mg. of urobilinogen per day. In hepatocellular jaundice, even when little or no bile is reaching the duodenum, the urinary urobilinogen is increased above normal, presumably because what little urobilinogen is formed in the bowel and absorbed cannot be re-excreted by the liver cells. Duodenal drainage reveals hypoconcentration of the bile in the acute phase. During recovery, the bile becomes hyperconcentrated. The serum bilirubin in the earliest phase may be of the indirect type, but soon more than 50 per cent is of the direct or "one-minute" type. The cephalin-cholesterol flocculation and thymol turbidity tests give positive reactions. The total serum cholesterol concentration is low in the acute phase and the esterified fraction is greatly reduced. During recovery the total serum cholesterol may increase even above normal.

Thus, in the earlier stages of this type of jaundice, some of the features of retention jaundice are present. As the parenchymatous disease advances, there may be such extensive changes in

the hepatic architecture that disorganization takes place, some of the bile passages become blocked, and regurgitation of bile occurs. Increased permeability of the cholangioles (the finer biliary radicles, especially the ampullae of the bile capillaries and the primary bile canaliculi in the portal spaces of the liver) leads to leakage or diapedesis of bile. This phase may be followed by recovery or the condition may advance to one of severe liver damage with atrophy. In the terminal stage a peculiar, somewhat musty or sweetish odor, the "foetor hepaticus," may be perceptible in the breath, and the liver functions are impaired to an extreme degree with even the blood urea nitrogen falling to values less than normal.

*Hepatocanalicular jaundice* is comparatively rare, forming perhaps but 4 or 5 per cent of all cases of hepatic jaundice. It may be the sequel of infectious hepatitis or it may follow the therapeutic use of arsenicals, sulfonamides, of thiouracil. Biliary cirrhosis (see p. 1488) can be classified with this group. Cholangiolitic hepatitis and cirrhosis are terms used by some writers to refer to certain cases of this type. In these the course is chronic and the jaundice of long duration. The hyperbilirubinemia is due chiefly to the presence of bilirubin of the direct or "one-minute" type. Duodenal drainage reveals hypoconcentration of the bile or acholia. Very low values for fecal urobilinogen are observed, and remain so for a long period of time. The urinary urobilinogen is normal when little or no bile is reaching the duodenum. The urine contains bile pigments and bile salts. The thymol turbidity and cephalin-cholesterol flocculation tests give essentially normal reactions while the total blood cholesterol and the serum alkaline phosphatase are increased. Biopsy reveals undamaged parenchymal cells, periportal infiltration, and no evidence of retention of bile.

*Posthepatitis jaundice* refers to jaundice produced by obstruction to the flow of bile in the bile ducts, usually the common bile duct. It may be *incomplete*, when it is usually due to stones in the biliary tract. Colic and chills, as well as pruritus, are often present in such cases. Incomplete posthepatitis jaundice can also be produced by postoperative or benign stricture of the common bile duct. Stricture, however, is much more apt to be followed ultimately by the development

of parenchymatous damage to the liver than is biliary lithiasis. The "one-minute" bilirubin generally forms over 60 per cent of the serum bilirubin. The fecal urobilinogen usually fluctuates, from very low to above normal. Bile pigment and bile salts are present in the urine and, at times, urobilinogen is found, even in increased amounts. The liver function tests which are usually positive in hepatocellular jaundice are, as a rule, normal in jaundice due to calculi. On the other hand, the alkaline serum phosphatase is greater than 10 units and the total serum cholesterol exceeds 200 mg. %. Duodenal drainage may reveal the "paradoxical syndrome": instead of the acholia expected from the other features of the case, a large amount of hyperconcentrated A bile is obtained. This is attributed to the stimulus produced by the tube in the duodenum, which releases the bile retained behind the obstruction.

In *complete posthepatic jaundice* more than 70 per cent of the serum bilirubin is generally of the "one-minute" type. The jaundice is usually produced by external pressure on the common bile duct and is most often due to carcinoma of the head of the pancreas. Similar jaundice is associated with carcinoma of the gallbladder, the ampulla of Vater, the main hepatic ducts, the common hepatic duct, and the common bile duct. A characteristic feature is the ever deepening character and the completeness of the biliary obstruction. The fecal urobilinogen becomes less than 5 mg. and the urinary urobilinogen less than 0.5 mg. per day. Exceptions to this rule are encountered, however, when the tumor is associated with edema or inflammation, which may recede, or when necrosis or hemorrhage occurs. In posthepatic jaundice due to carcinoma, the liver function other than that concerned with excretion is good except when very long-standing obstruction has led to damage to liver cells or when hepatic metastases are very extensive. Thus the alkaline phosphatase and the plasma cholesterol are increased, but the cephalin-cholesterol flocculation, thymol turbidity, and galactose tolerance tests are normal. If the plasma prothrombin is low, it is due to faulty absorption of vitamin K resulting from lack of bile in the bowel, as can be shown by the rise in plasma prothrombin following the intravenous administration of vitamin K. Pruritus is pronounced, as it is whenever whole bile is returned to the blood.

### STUDY OF A CASE OF LIVER DISEASE

Since a discussion of the functions of the liver, and the description of methods for testing these functions, can easily give the impression that the study of a case of hepatic disease is essentially one requiring elaborate technical aid, it must be pointed out that much can be done by the application of the fundamentals of good medical practice and, at most, by the use of very simple laboratory procedures. By this it is meant that much can be learned from a carefully taken history and a thorough physical examination. Important supplements are the appearance of the urine to the naked eye and the color of the stools as obtained by digital rectal examination.

**X** The history must give attention especially to possible exposure to hepatotoxic agents and to parenteral injections, especially of blood and blood products. **II** If pain is present, a detailed analysis may suggest biliary colic or the pain may be found to be of the less well-defined type seen in carcinoma of the pancreas. The latter is not rarely mistaken as being functional in origin. The **I** physical examination should seek out the vascular spiders, usually on the face, upper extremities, and shoulders, which, in the presence of signs of liver or biliary tract disease, are almost pathognomonic of parenchymatous liver involvement; the presence of edema, which may be due to the effect of back pressure or may be the result of hypoalbuminemia or of an excess of antidiuretic hormone; and the existence of icterus, which may not be obvious without careful examination of the scleras. Evidence of scratching will be found if there is pruritus. That this symptom is due to the retention of bile acids or their salts is suggested by the fact that pruritus is not associated with pure hemolytic jaundice. **II** Enlargement of the liver suggests, in particular, cirrhosis, carcinoma, or syphilis. **II** Splenomegaly is found in hemolytic jaundice and in association with primary liver disease, such as cirrhosis or hepatitis. Enlargement of the spleen is rare otherwise in association with jaundice, except in cases of cancer of the pancreas, when it is encountered in one fourth of the cases. **II** A distended and palpable gallbladder which is smooth and not tender suggests carcinoma as the cause of the jaundice. The jaundice of hepatitis tends to be golden orange in

Table 14

## USUAL RESULTS OF LIVER FUNCTION TESTS IN VARIOUS TYPES OF JAUNDICE

Tests	Normal	Prehepatic Jaundice		Hepatic Jaundice		Posthepatic Jaundice	
		Hemolytic	Non-hemolytic	Hepato-cellular	Hepato-canalicular	Incomplete	Complete
<b>BILE PIGMENTS</b>							
Serum bilirubin							
"One-minute," mg.....	0.2	0.2	0.2	30-50 %	60 %	60 %	70 %
Total, mg.....	0.8	1-10	1-4	1-12	2-20	7-30	7-45
Urine bilirubin.....	0	0	0	++	+++	+++	++++
Urobilinogen							
Urine—semiquan., units	0.5-1.5	5-60	N	0 or +++	0 or +	0 or +	0
U.U., mg./day.....	0-3.5	1-200	N	10-300	1-5	0-50	< 0.5
Stool—semiquan., units							
per 100 Gm.....	< 350	+++	N	0 or +	0 or +	0 or +	0
F.U., mg./day.....	40-280	300-4000	N	10-300	0 or +	10-600	< 5
<b>OTHER EXCRETORY FUNCTIONS</b>							
Bromsulfalein, % retention..	0	0	0			Of no value when obstruction is present	
Hippuric acid excre.,							
oral, Gm.....	> 3						
intravenous, Gm.....	> 1}	N	N	Dec.	N or dec.	N	N
<b>PROTEIN METABOLISM</b>							
Serum albumin.....	5.0	N	N	Dec.	N or dec.	N	N or dec.
Serum globulin.....	2.0	N	N	++	N	N	N
A/G.....	2.5	N	N	Rev.	N	N	N
Cephalin-cholesterol							
flocculation.....	Neg.	Neg.	Neg.	++++	+	Neg.	Neg.
Thymol turbidity, units.....	3-4	N	N	10-40	4-10	N	N
<b>CARBOHYDRATE METABOLISM</b>							
Galactose tolerance,							
oral, Gm.....	< 3	N	N	> 3	N	N	N
intravenous, mg.....	< 20	N	N	> 20	N	N	N
<b>FAT METABOLISM</b>							
Cholesterol							
Total, mg./100 ml.....	120-300	N	N	N or +	++	++	+++
Free.....	..	N	N	++	++	++	+++
Esters, %.....	66-78	N	N	Dec.	++	++	+++
<b>MISCELLANEOUS FUNCTIONS</b>							
Alkaline serum phosphatase,							
Bod. units.....	1-4	N	N	N	> 10	> 10	> 10
Vitamin K test, % iner. in							
prothrombin 24 hours after							
2 mg.....	> 20	N	N	< 20	N or dec.	N	N
<i>Remarks</i>							
> means "greater than"	..	Anemia,	..	Biliary obstruction incomplete.		Intermittent disturbance in pigment excretion.	Steadily increasing serum bilirubin
< means "less than"		reticulo-		Splenomegaly.		Colic.	and steadily decreasing stool urobilinogen.
0 means "absent"		cytosis,		Vascular spiders		Chills	Pruritus.
+	means "present"	splenomegaly					Gallbladder distended
++ or +++ or +++++							
means "increased"							
N means "normal"							
Neg. means "negative"							
Dec. means "decreased"							
Rev. means "reversed"							

hue; that due to posthepatic obstruction, blackish or greenish. Melanosis of the skin is seen in biliary or cholangiolitic cirrhosis.

Of the *laboratory procedures*, the Harrison spot test for bilirubinuria, the semiquantitative tests for urobilinogen in the urine and stools, the thymol turbidity test, and the icterus index should be mentioned as being applicable in most laboratories. For the detection of hepatic disturbance in the early stages of infectious hepatitis, bromsulfalein retention and bilirubinuria have proved to be of great value. It is helpful to remember that bilirubinuria is related to the presence in the plasma of the "one-minute" or prompt-reacting type of bilirubin which has passed through the liver cells and is being regurgitated. The tests concerned with alterations in protein metabolism (cephalin-cholesterol, thymol turbidity) are most useful in following the course of parenchymatous liver disease. The bromsulfalein test is of no value in the face of posthepatic jaundice.

Since parenchymatous disease of the liver can produce deep and persistent jaundice, much care is needed for differentiation from posthepatic jaundice due to carcinoma or biliary calculi. The presence of more than 5 mg. per day of fecal urobilinogen favors stone or parenchymatous disease rather than carcinoma, and a disproportionate amount of urinary urobilinogen as compared with fecal favors parenchymatous disease. When the latter exists, the total cholesterol may be increased or decreased but cholesterol esters are likely to be greatly reduced, and the cephalin-cholesterol flocculation and thymol turbidity tests are positive. In the presence of parenchymatous disease, in addition to obstruction, both the "one-minute" and the "indirect" serum bilirubin are increased. In the absence of parenchymatous disease the prothrombin level of the blood is normal or, if low as the result of impaired absorption of vitamin K, rises in response to the intramuscular administration of the vitamin.

The comments which have been made in this section should have made it clear that repeated examinations are of great value in diagnosis as well as in observing the progress of the patient. The simplest laboratory procedures, furthermore, if carried out accurately, are more useful than less carefully performed though seemingly more important and more complicated ones. Thus, when jaundice is due to a biliary stone, the icterus index will usually become steadily greater;

in the majority of cases of hepatitis, the icterus index will at first become greater and then lower and lower values will be found as recovery takes place.

A useful aid in the differential diagnosis of jaundice is the duodenal tube, if facilities exist to determine roentgenoscopically that the tip of the tube has been located correctly. Thus the demonstration of blood and the absence of bile strongly suggest carcinoma as the cause. The "paradoxical syndrome" of biliary stone has been mentioned already.

Gallbladder visualization by x-ray examination is of no value in the differential diagnosis of jaundice, but the demonstration of stones in the biliary tract or pancreatic duct by means of a flat film, the finding of widening and distortion of the duodenal loop as is seen in pancreatic carcinoma, and the visualization of esophageal varices in cirrhosis of the liver, are useful procedures.

The histologic examination of liver tissue removed by needle biopsy is proving to be helpful in cases in which the diagnosis is not clear. This procedure is not without danger, however, and should not be carried out when there is any form of bleeding tendency, such as reduced prothrombin time, when there is hepatic congestion, or when the patient cannot or will not coöperate.

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## Disordered Renal Function

M. F. Mason and T. R. Harrison

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### General Principles

Disturbances of Renal Function

Reversibility of Renal Failure

Approach to the Patient with Renal Disease

### Clinical Manifestations of Disorders of the Urinary System

Disorders of the Act of Urination

Disturbances in Volume of Urine

Alterations in Composition of Urine

Uremia

### GENERAL PRINCIPLES

The primary functions of the kidneys are excretion and conservation. Thus the kidneys constitute the chief channel by which the end products of metabolism other than carbon dioxide—i.e., water and a variety of solutes—are removed from the body. The mechanisms involved permit the selective excretion of those substances no longer needed in the body economy, with simultaneous conservation of those for which there is further use. These processes supplement one another so that, in health, relative constancy of the composition of the internal environment is maintained. In addition, there are certain metabolic functions of the kidneys which contribute to both conservation and excretion. Gradual evolutionary adaptation has resulted in the present organ, which is remarkably suited to meet the obligations imposed upon it under the environmental circumstances to which man is subjected. The chief feature of the mammalian kidney is its ability to secrete a urine which is simultaneously hypertonic and hypotonic in respect to different solutes, so that the composition of the body fluids remains unaltered, in health, over wide ranges of water and food intake.

The formation of urine by the kidney is the summated result of function of individual nephron units, of which there are about 1,300,000 in each kidney. The nephron unit comprises the glomerulus with its subjoined tubule, the latter connecting with the larger collecting tubules which drain into the renal pelvis. The blood supply to each nephron unit enters via an afferent

arteriole and, after traversing the capillary network contained within the glomerulus, passes via an efferent arteriole into a peritubular network of capillaries which ultimately drain into the renal vein. Means are thereby provided for producing marked alterations in intraglomerular pressure and in volume flow of blood to the nephron. The permeability of the glomerular capillaries permits the formation of a plasma ultrafiltrate, amounting to about one fifth of the volume of the plasma perfusing the glomerulus per unit time. This ultrafiltrate, which pours into the proximal convoluted tubule, is essentially free from protein (see below), but contains the crystalloids in the same concentrations as they were present in the arterial plasma. During the passage of the glomerular filtrate along the tubule, this fluid is modified to urine by tubular reabsorption of most of the water and variable portions of many of the solutes, and by additional secretion of other solutes by the cellular structures lining the tubule, these solutes having been abstracted from the plasma of the peritubular circulation. The sole function of the glomeruli is excretion; the tubules play a much less important excretory role, their predominant function being conservation. Only a few naturally occurring metabolites are as yet known to be removed from the body by tubular excretion.

The solutes of urine may be divided conveniently into three categories: (1) *threshold bodies* whose plasma concentrations are carefully guarded and which fail to appear in the urine at plasma concentrations below certain limits—e.g., glucose and chloride; (2) *nonthreshold bodies* which appear in the urine at any finite plasma concentrations—e.g., various foreign dyes, hippuric acid; (3) *variable threshold bodies* whose plasma concentrations are not carefully regulated by subsequent tubular activity—e.g., urea and sulfate.

A striking feature of the kidneys is the volume of their blood supply, which amounts, in the average-sized adult at rest, to about 1200 ml. per minute—i.e., about one fourth of the resting cardiac output. The renal blood flow is measured by introducing a renally excreted solute such as "Diodrast" or para-amino hippurate into the circulation at a rate which provides a plasma concentration so low that all of the substance is removed in the initial passage of the plasma through the kidneys. The "effective" volume flow of blood per unit time is readily calculated if the mean plasma concentration, hematocrit reading, and the urine output of the substance over a given period are measured. Thus if, at a mean plasma concentration of 0.02 mg./ml. para-amino hippurate, urine contained 3 mg./ml. of the solute while forming at a rate of 4 ml./min., then in one minute 12 mg. of para-amino hippurate was provided to the kidneys in the plasma. Hence, a minimum of  $12/0.02$ , or 600 ml., of plasma must have perfused the kidneys in one minute, and if the hematocrit reading were 40 per cent, then  $600/0.60$ , or 1000 ml., was the total minute-volume flow of blood. Actually, it is found that not quite all of the solute employed is removed, even at very low concentration. This is taken to indicate that a small amount of the blood, some 5 to 10 per cent of the total, perfuses nonexcretory tissue, and is not "effective" in relation to renal excretory function. In addition, there appears to be a small quantity of the effective blood flow which by-passes the glomeruli and perfuses only the tubular bed. This fraction may be markedly increased in disease in which the glomeruli are injured.

When the renal blood flow is normal, the corresponding glomerular filtration rate in the average-sized adult amounts to about 130 ml. per minute (i.e., about 180 liters per 24 hours). This may be determined by introducing into the circulation a substance which is filtered at the glomerulus but which is neither reabsorbed from nor secreted into the tubular urine, and measuring the plasma and urine concentrations and the volume of urine secreted per minute. The filtration rate is then calculated from the expression  $\frac{U}{P} \cdot V = C$ , in which  $U$  is the urine concentration,  $P$  is the plasma concentration, and  $V$  the volume of urine passed per minute.  $C$  is also the "clearance" of the solute as well as (in this instance)

the glomerular filtration rate, representing the equivalent of the volume of plasma which may be stated to have been completely cleared of the solute in one minute—i.e., the volume of plasma which contained the quantity of solute found in the urine secreted during one minute. Inulin (a polysaccharide), mannitol, and certain other hexitols are suitable solutes for this measurement.

In the case of a substance which is filtered by the glomerulus and partly reabsorbed from the tubules, the proportion reabsorbed is directly estimated by comparing its measured clearance, as

defined by the expression  $\frac{U}{P} - V$ , with the simultaneously determined glomerular filtration rate.

For example, if the glomerular filtration rate were 130 ml., and the clearance of urea were found to be 75 ml., the latter would be  $75/130 \times 100$ , or approximately 60 per cent of the former, indicating that about 40 per cent of the urea filtered must have been reabsorbed during passage through the tubules. The absolute amount of solute reabsorbed per unit time may be calculated, and recently it has been shown for a number of solutes that, as the quantity presented to the tubules to reabsorb is increased (by raising the plasma level), a maximum rate of reabsorption is reached beyond which no further increase may be attained, this rate constituting the tubular maximum ( $T_m$ ) for the solute concerned. The value is clearly dependent upon the number of functional nephron units, and the capacity of function of these.

When excretion of a solute is the consequence of tubular secretion, the clearance may be calculated from the same measurements mentioned previously. In this case, the calculated clearance is a function of the plasma level of the solute, and with plasma levels sufficiently low so that all the solute is removed in one passage through the kidneys, the clearance equals the renal plasma flow. Again, the absolute amount of solute secreted may be calculated, and as the plasma concentration is increased the quantity secreted by the tubules increases, and finally attains a maximum beyond which no further increase occurs. This is the tubular maximum ( $T_m$ ) for the solute concerned. Thus it is known that a plasma para-amino hippurate concentration of 0.75 mg./ml. is well above that at which no further increase in its tubular secretion occurs. If, at that plasma level, the urine contained 37 mg./ml., at a vol-

ume of 4 ml./min., then  $4 \times 37 = 148$  mg. of para-amino hippurate was excreted in one minute's time. But some of this was filtered at the glomerulus, and if the measured filtration rate were 130 ml./min., and if 83 per cent of the para-amino hippurate were free for filtration (i.e., not protein-bound), then  $0.75 \times 0.83 \times 130 = 81$  mg./min. were excreted by filtration, and  $148 - 81 = 67$  mg./min. represents the maximum mass of solute which was secreted by the tubules (= T<sub>m</sub>, para-amino hippurate). Presumably, constancy of the observed T<sub>m</sub> is the consequence of saturation of the mechanisms involved in the transfer of the solute from the tubular epithelial cell into the urine. It follows that the value of the T<sub>m</sub> depends upon the number of functioning tubules, and the summated capacities of each of them to excrete the particular solute.

Only some 0.5 to 2 per cent of the enormous volume of glomerular filtrate normally reaches the bladder as urine, as almost all the water is reabsorbed in the passage of the filtrate down the tubule. This reabsorption of water may conveniently be divided into two phases. The first is the obligatory reabsorption of an essentially isosmotic fluid which takes place in the proximal convoluted tubule, and consists of the back diffusion of about 80 to 90 per cent of the water, and a number of solutes. This reabsorption is apparently the consequence of the decline in pressure in the peritubular capillaries, and of the increased osmotic pressure in the peritubular plasma, caused by the increase in its protein content as a result of the filtration of the fluid in the glomerulus.

The second phase is facultative in that the remaining 10 to 20 per cent of the water may be mostly saved or mostly discarded, depending upon the needs of the organism. The degree of facultative reabsorption is controlled largely by the antidiuretic hormone from the posterior pituitary gland. The secretion of this hormone apparently takes place in response to stimuli originating in the hypothalamic area, and those in turn are elicited by hypertonicity of the circulating plasma, by pain, excitement, various conditioned reflexes, anesthetics, etc. Hypotonicity of the plasma tends to inhibit the release of the hormone, and hence causes diuresis. Certain sensory stimuli have a similar effect. In the absence of regulation by the antidiuretic hormone,

the urine volume attains a magnitude of 25 to 30 liters per day (complete diabetes insipidus). On the other hand, excessive secretion of the hormone produces diminution in urine output to low levels, the limiting value being determined by the maximum capacity of the tubular cells concerned to concentrate urine—i.e., by the maximum osmotic gradient which may be achieved. The locus of action of the hormone appears to be confined to the thin loop of Henle, or to the distal convoluted tubule. It should be noted that, while the conservation or discarding of water may, in a sense, be considered independent of the clearance of various solutes, actually, the latter are often affected considerably. Thus the clearance of urea falls markedly as the urine volume diminishes to low levels, and the output of chloride usually increases considerably with antidiuresis.

One of the important conservational functions of the kidney is that of retaining sodium while simultaneously discarding acid anions which would otherwise be secreted in the urine as alkali salts. This conservation is necessary if the volume and concentration of extracellular fluid are to be defended, and is the result of two effects. The first is the secretion of an acid urine. In this case the acidity of the urine is a direct measure of the base saved, in that hydrogen ions have been substituted for alkali cations as the glomerular filtrate has been modified from pH 7.4 to the final pH attained. This conservation is largely the result of altering the ratio of inorganic phosphate excreted as the monobasic and dibasic salts by increasing the proportion of the former, and of elimination of a greater proportion of urinary organic acids as the free acids rather than as salts. The second mechanism involved is the substitution of ammonia for alkali cation by the renal tubular epithelial cells. The sources of the ammonia are certain amides, chiefly glutamine, and possibly asparagine, whose presence in body fluids is the consequence of competition by the dicarboxylic amino acids, glutamic acid, and aspartic acid with ornithine for ammonia formed by deamination (chiefly in the liver) with the formation of the corresponding amides. Most of the ammonia released by deamination is, of course, converted into urea. Hydrolysis of these amides by specific enzymes in the tubular cells releases the amide nitrogen as ammonia, the rate of this process being determined, in part, by the acidity of the tubular urine.

## DISTURBANCES OF RENAL FUNCTION

Functional impairment of the kidney may be classified from several different points of view, as illustrated in the following outline:

1. From the viewpoint of morphology, according to whether the primary alteration in architecture affects the vascular, glomerular, or tubular component of the nephron
2. From the viewpoint of pathogenesis:
  - a. Primary disorder of the kidney
  - b. Secondary disorders of the kidney, the primary disorder being elsewhere ("prerenal deviation," "prerenal azotemia")
3. From the viewpoint of severity:
  - a. Early impairment of function; i.e., diminished homeostatic capacity occurring only under conditions of increased load
  - b. Advanced impairment of function (renal insufficiency); i.e., failure of homeostatic capacity (under conditions of either normal or diminished load)
4. From the viewpoint of prognosis:
  - a. Irreversible impairment (usually the result of organic damage, acute or chronic extensive destruction of nephron units)
  - b. Reversible impairment (resulting either from primarily extrarenal disorders, or from acute renal disease without extensive destruction of nephron units)
5. From the viewpoint of the specific function involved:
  - a. Alterations in renal blood flow
  - b. Alterations in glomerular filtration
  - c. Alterations in tubular capacities
  - d. Alterations in metabolic capacities

The discussion to follow will approach the subject, in the main, from the last-mentioned viewpoint, but especially pertinent aspects of the other viewpoints will also be considered.

Disordered renal function may be considered broadly to be the consequence of alterations in one or more of the several capacities of the kidney—i.e., the glomerular filtration rate, rate of tubular reabsorption of water or various solutes, rate of tubular secretion of various solutes, or rate of metabolic functions. These changes are secondary to a variety of causes, some of which are described in more detail below.

It is convenient to consider, arbitrarily, a

measurable deviation from the normal range of one or more of these capacities as representing "impairment" in respect to the function or functions involved. If this is of such degree that homeostasis of the internal environment cannot be maintained when average normal loads in terms of solutes and water are presented for glomerular filtration, tubular reabsorption, and excretion, then the kidney is "insufficient" in respect to the functions concerned. It should be clear that no sharp separation may be made between impairment and insufficiency, inasmuch as maintenance of homeostasis is dependent upon load. Indeed, the normal kidney may be an insufficient kidney in the sense that homeostasis is not maintained under loads of sufficient magnitude—e.g., the relative azotemia accompanying high-protein diets with low water intake, water intoxication following excessive intake of water, etc.

**1. Diminution in Renal Blood Flow.** Such a decline frequently results from disorders which are initially of extrarenal origin, and especially from conditions which cause circulatory failure. When diminished renal blood flow is intrinsically renal in origin, it is the result of either destruction of glomerular tufts, arterial disease involving the subdivisions of the renal artery and particularly the afferent arterioles, exaggerated afferent and/or efferent arteriolar tonus, or increased intrarenal pressure due to renal edema or associated with obstructive nephropathy. These various disorders limit the amount of blood which may be perfused through the kidney at a normal arterial pressure, with resultant peritubular ischemia which may lead to tubular dysfunction—i.e., diminution in capacity to perform osmotic work, with ultimate replacement of nephron units by fibrous tissue. The glomerular filtration rate may also be lowered, although, because it is so largely dependent upon intraglomerular pressure, this function may be normal or even increased in spite of marked declines in renal blood flow. The extent to which irreversible functional or architectural changes occur seems to be determined largely by the degree and duration of the diminution in flow of blood through the kidneys.

**2. Alterations in Glomerular Filtration Rate.** At the present time there is no evidence that abnormal increase in filtration is of clinical importance. The filtration rate may decline from the normal volume of about 130 ml. per minute,

as a result of several causes. The most important of these are conditions, already mentioned, which cause decline in renal blood flow per nephron, and conditions which cause diminution in the total number of nephron units. Theoretically, filtration can be hampered by thickening of the glomerular tufts, but it is probable that such a change is usually accompanied by decline in renal blood flow. It is likewise possible that alterations in glomerular capillary pressure, unattended by changes in blood flow, would cause decline in glomerular filtration. This mechanism is probably of little or no clinical importance. The reverse mechanism, in which, despite a decline in the renal blood flow, the glomerular filtration rate is well sustained as the result of constriction of efferent arteriolar vessels, with rise of glomerular capillary pressure, is of great importance in maintaining renal function.

The degree to which the filtration rate may fall without producing failure of homeostatic maintenance is a function of the load of solutes and water presented for excretion and the functional capacity of the tubules. Thus, if the tubules are unimpaired and the load is small, the filtration rate may fall to a rather small fraction (e.g., one fifth or one sixth) of its normal value without alterations in the composition of body fluids. On the other hand, with impairment of tubular capacities and greater loads, then not only may there be retention of those substances having the highest concentration ratios ( $\frac{U}{B}$ ), but, in addition, changes in composition of body fluids may occur as the result of failure selectively to retain or excrete sodium, chloride, bicarbonate, phosphate, etc., or to form ammonia or conserve base by the secretion of an acid urine. There is some evidence that diminution in filtration rate of sufficient degree in a nephron, without accompanying impairment of tubular function, may produce a glomerular-tubular imbalance in the sense that the actively functioning tubule blindly reabsorbs solutes and water from a smaller volume of glomerular filtrate, with consequent retention and augmentation of the quantities of these in the body. This hypothesis has been invoked to explain the retention of salt, water, and various nitrogenous solutes in acute glomerulonephritis.

**3. Alterations in Tubular Capacities.** Tubular ischemia from any cause, if sufficiently severe or

prolonged, or tubular damage consequent to inflammation, or the local effects of various nephrotoxins, may produce diminution in capacity of these specialized structures to reabsorb effectively solutes against osmotic gradients, or to secrete solutes at a normal rate. Concomitant failures to reabsorb water against an osmotic gradient results in the development of isosthenuria—i.e., fixation of gravity at essentially that value characteristic for the unmodified glomerular filtrate. Certain solutes, such as sodium and chloride, when their rate of intake is low, must often appear in the urine in smaller concentrations than in the glomerular filtrate, if electrolyte loss from the body is to be avoided. Failure to render the tubular urine hypotonic in respect to these solutes results in loss of salt and water from the body, and extracellular fluid deficit, as well as distortion from normal of the actual concentrations of the various electrolytes in the body fluids, if the rate of intake of the respective solutes is slower than their rates of renal excretion.

The reductions in tubular capacities may simultaneously involve a number of solutes and water, or may, in certain relatively rare instances, be confined to a single solute. In this instance tubular ischemia or discrete tubular disease, detectable by architectural change, does not appear to be concerned, and the causative factors are not yet precisely described. For example, in patients with Addison's disease there is a failure to reabsorb sodium adequately from the glomerular filtrate, and the loss of this, if sufficiently great, will lead to extracellular fluid deficit and peripheral circulatory failure. Patients with renal glycosuria (diabetes innocens) exhibit a marked reduction in the glucose T<sub>m</sub>; i.e., they cannot entirely reabsorb the glucose filtered at the glomerulus at normal levels of plasma sugar, and hence exhibit variable degrees of glycosuria in the fasting state, and more exaggerated degrees thereof during postalimentary hyperglycemia. This defect, superimposed upon a defect in the tubular modification of urine in respect to phosphate, chloride, and bicarbonate, constitutes the chief derangement in the Fanconi syndrome.

Certain poisonous agents may specifically damage tubular epithelial cells, thus reducing their capacities. Uranium, mercury, and phlorhizin are notable examples of these.

One of the interesting developments in renal physiology has been the apparent demonstration that the energetic systems responsible for the osmotic work in secretion or reabsorption are in some instances the same for different solutes, and increasing the load factor in respect to one solute may diminish the amount of the other which may be handled simultaneously. Thus the administration of the solute *p*-amino hippuric acid, secreted by the tubules, causes a decline in the rate of tubular secretion of penicillin by the same energetic mechanisms, so that a given dose of the antibiotic persists in the body for a considerably longer time, as a result of the successful "competition" for excretion by the *p*-amino hippurate. It may be that a similar situation accounts for the increase in proteinuria which is observed with hemoglobinuria following intravascular hemolysis.

It should be clear that the maximum tubular excretory rate for a given solute may be reduced by simple reduction in the number of functioning nephrons, as well as by reduction in the inherent energetic capacities; i.e., irreversible diminution in tubular capacity is brought about by circumstances ranging from those which convert the tubule to a relatively inert conduit for one or more solutes and water, to those which result in its obliteration and replacement by scar tissue.

**4. Alterations in Metabolic Capacities.** The intermediary metabolic functions of the kidneys, other than that of ammonia synthesis, are little understood. The latter function, however, is a late feature of irreversible failure of a nephron, in that considerable reductions in the various other tubular capacities usually have occurred before the decline in ability to form ammonia, and to substitute this for alkali cation, is marked. When, however, limitations in the ammonia mechanism do occur, they are of great import, as the organism is proportionately deprived of one of its most important defenses for maintenance of constancy of the internal environment. The resulting further failure to conserve base adequately rapidly exaggerates the distortions in concentrations and volumes of body fluids (see Chapter 29), and renders treatment of these profoundly difficult.

#### REVERSIBILITY OF RENAL FAILURE

From a practical standpoint it is of special importance that reversible renal insufficiency be

recognized in order that vigorous treatment may be substituted.

A number of circumstances involving extrarenal derangements may secondarily or directly bring about reductions in one or more of the various renal capacities, ranging from impairment to insufficiency. Such alterations are frequently implied by the terms "prerenal deviation" or (if there are concomitant increases in the concentrations of nonprotein nitrogenous constituents of body fluids) "prerenal azotemia." If the capacities of the kidneys are already irreversibly limited, the effects of such extrarenal factors are greater in magnitude. In any event, reversible renal failure of this sort, whether *de novo* or superimposed upon some degree of irreversible failure, is characterized by amelioration upon correction of the primary factor initiating its onset, providing the duration has not been so long that irreversible damage has occurred to a significant number of nephron units.

Common causes of reversible failure are peripheral circulatory failure (Chapter 14) and, less commonly, congestive heart failure. For example, acute profuse hemorrhage into the gastrointestinal tract is one of the commonest causes of reversible renal failure. The immediate consequence of a diminution in renal blood flow, of a degree too great to be compensated by reflex adjustments in tonus of the afferent and efferent arterioles, is a decline in glomerular filtration rate. Hence the urine volume is low or scanty and specific gravity normal to unusually high. Persistence of the accompanying tubular ischemia and anoxia eventually results in a decline in capacity for performance of tubular osmotic work, and this is reflected in the corresponding decline in specific gravity of the urine, irrespective of the volume excreted. The rate at which azotemia develops may be augmented greatly by a concomitant increase in the rate of protein catabolism—e.g., as with fever. In febrile states direct but usually reversible organic damage to nephrons may occur.

Even in the absence of alterations in blood pressure, declines in renal functional capacities may also result from vasomotor reactions secondary to painful stimuli, or from administration of anesthetic agents. In these instances the renal manifestations are, presumably, the result of a redistribution of the volume flow of blood to various organs at the expense of the kidneys,

and/or an exaggerated response of the posterior pituitary-hypothalamic mechanism governing the excretion of water. A direct effect of anesthetics upon tubular energetic mechanisms has not yet been excluded as being of some importance.

Alterations in filtration rate, with changes in plasma protein concentration, are rather small over the range of protein concentrations usually encountered in either health or disease, probably as a result of the neat adjustment of intraglomerular pressure which may be achieved by vasomotor control. If the latter is inadequate, then fluctuations in plasma protein may cause significant changes in filtration rate. In the presence of profound experimental hypoproteinemia the filtration rate, contrary to superficial expectation, may sharply decrease, presumably because of the associated edema of the kidney with mechanical hindrance to the flow. Such a mechanism may be operative in certain instances involving hypoproteinemia clinically.

In a number of instances actual architectural alterations accompanying functional disturbances appear to be reversible. Thus, acute glomerulonephritis may subside, and with the return of functional capacities there may also be a complete restitution of normal architecture. A similar situation appears to obtain in respect to the lower nephron nephroses accompanying transfusion, reactions, crushing injuries, and acute liver insufficiency, and to the perhaps less striking tubular damage following prolonged ischemia and/or anoxia, or accompanying acute febrile states. Perhaps the most significant factor determining the reversibility of these states is the duration of the initiating circumstances. It has recently been shown that renal damage, previously thought to be irreversible in nature, may be reversible by virtue of tubular regeneration, providing methods of treatment employed are adequate to assure survival of the patient for a sufficient period of time.

It may be seen, from the foregoing discussion, that the distinction between reversible and irreversible disorders of renal function is not always a clear one. In any event, it is of importance, in a given patient, to assess renal functional status, and to determine whether or not the circumstances causing any diminution are possibly reversible in nature, when appropriate treatment is instituted.

## APPROACH TO THE PATIENT WITH RENAL DISEASE

From the foregoing discussion it appears that it is now possible to quantitate, in a given patient, such functions as renal blood flow, glomerular filtration rate, and a number of the specific capacities of the renal tubules to reabsorb or secrete a variety of solutes and water. The facilities for such measurements, however, are at present only rarely available, and the renal status of most patients must be assessed on the basis of the history, the physical findings, and the examination of the urine. Certain additional renal function tests, which may be done readily in the physician's office or in the usual hospital laboratory, are also important.

In evaluating the renal status, three questions must be answered:

**1. Is Renal Disease Present?** The answer to this question will come largely from the examination of the urine (which should be collected by catheter in the female) and especially from the detection of proteinuria which cannot be accounted for on the basis of posture, fever, disease of the lower urinary tract, etc. The presence of erythrocytes or leukocytes in the urine can be interpreted as almost certain evidence of disease of the kidneys, rather than of the lower urinary tract, only when casts in abnormal numbers are also found in the urine. The significance of these several abnormalities of the urine will be discussed in more detail later, but it may be emphasized here that orthostatic and febrile proteinuria should be eliminated before conclusions are drawn concerning renal disease as a cause of proteinuria.

**2. If Renal Disease Is Known to Be Present, Is It Active and Progressive?** The answer to this question, likewise, is to be found in the examination of the urine. Leukocytes and (especially) erythrocytes in large numbers usually indicate an active process. Casts containing cells have a similar significance; hyaline casts are often present when the process is essentially stationary; granular casts are of intermediate import. The amount of protein present is related to the type of renal disease but is not well correlated with its activity.

**3. How Severe Is the Impairment of Excretory Function?** It is here that certain special but simple tests are of value. When facilities are

available, the urea clearance test or the endogenous creatinine clearance test yields valuable information concerning impairment of glomerular filtration. Estimation of tubular capacity to perform osmotic work by the determination of maximum concentrating power (i.e., the highest specific gravity obtainable after several hours of water deprivation, following a high-protein meal) is a valuable and simple procedure. Since concentrating power becomes impaired at a relatively early stage of chronic renal disease, this test is especially useful in the less advanced instances.

When some reduction in concentrating power is demonstrable, the conventional phenolsulfonphthalein test yields additional information. This test is, in the main, a measure of the limitation of tubular excretory capacity imposed by diminished renal blood flow. (In the presence of liver disease abnormally high values may be obtained.)

These two procedures will demonstrate excretory impairment before excretory failure occurs. The latter is detected by measurement of the nitrogenous components of the blood (urea, creatinin, nonprotein nitrogen). Once these begin to be elevated, excretory impairment has progressed to excretory failure, and the degree of failure can be better estimated by study of the blood than by study of the urine. The concentration test is, therefore, the most valuable of the simple procedures in the earlier stages, and the measurement of nitrogenous constituents of the blood the best guide in the later stages of renal disease. It should be emphasized, however, that the absolute levels of functional tests are much less important than the trend of the levels over a period of time, and that laboratory data are often meaningless unless interpreted in the light of the clinical picture.

### CLINICAL MANIFESTATIONS OF DISORDERS OF THE URINARY SYSTEM

The phenomena which develop as the result of disturbances in the excretion of urine may be divided into several general groups, according to the following outline:

1. Disorders of the act of urination:
  - a. Dysuria (i.e., pain, or difficult urination)
  - b. Frequency

- c. Hesitancy
  - d. Incontinence and dribbling
  - e. Nocturia (or nycturia; i.e., necessity for urination during the normal period of sleep)
2. Disturbances in volume of urine:
    - a. Polyuria (i.e., increased volume of urine)
    - b. Oliguria (i.e., decreased volume of urine) and anuria (i.e., cessation of urine flow)
  3. Alterations in composition of urine:
    - a. Proteinuria and cylindruria (i.e., casts in the urine)
    - b. Hematuria (i.e., blood in the urine)
    - c. Pyuria (i.e., leukocytes in the urine)
    - d. Various chemical alterations (discussed in Chapters 28, 29)
    - e. Hyposthenuria (i.e., diminution in concentrating power)
    - f. Isosthenuria (i.e., loss of ability to form a concentrated or a dilute urine)
    - g. Changes in the colloidal state of urine (nephrolithiasis)
  4. Systemic manifestations of altered renal function:
    - a. Hypertension (Chapter 13)
    - b. Edema (Chapter 20)
    - c. "Dehydration" (Chapter 28)
    - d. Uremia
    - e. Other changes in composition of body fluids (Chapter 29)

### DISORDERS OF THE ACT OF URINATION

**Dysuria.** Of these disorders, the most common is dysuria, which may be defined as difficult or painful urination. In general, this symptom is brought about by disorders of the lower, rather than the upper, urinary tract. Any inflammatory process or obstruction in the urethra, bladder, or lower ureter may produce dysuria. The various types of cystitis (especially those involving the trigone), gonococcal urethritis, and stones in the bladder and lower ureter are among the most frequent causes of dysuria. The symptom is likewise induced by disorders which cause obstruction to the passage of urine from the bladder through the urethra. Benign enlargement of the prostate, carcinoma of the prostate, and urethral stricture as the result of previous gonococcal urethritis are common causes.

**Frequency of urination** may be brought about by any of the conditions which cause dysuria,

and, in addition, is commonly observed during states of excitement, agitation, or anxiety. The various conditions, discussed later, which cause polyuria may also cause frequency.

**Hesitancy of urination** may likewise be psychogenic in origin, and commonly appears in sensitive and introspective subjects during urination in public toilets. The more important causes of hesitancy are the conditions which produce obstruction to the free outflow of urine; of these, benign prostatic hypertrophy is most frequent.

**Urinary incontinence**—i.e., a state in which urine is voided involuntarily—is a normal phenomenon during infancy, and persists in some children for a number of years, in the form of nocturnal incontinence, or enuresis. The symptom may likewise appear in adults during severe fright. Incontinence of urine is frequently observed in comatose states, and in patients with extensive disease of the spinal cord. When due to any of the conditions which have been mentioned, it is not associated with dysuria. Incontinence is also frequently the result of local disorders of the bladder and urethra.

**Nocturia**, although in a strict sense a disturbance in the act of urination, is frequently induced by disorders which affect the volume of urine, and will therefore be discussed subsequently (see below).

#### DISTURBANCES IN VOLUME OF URINE

**Polyuria.** Since 96 to 99 per cent of the water which filters through the glomeruli is normally reabsorbed, a relatively small change in reabsorption will cause a relatively large alteration in urine volume, and hence it is almost always the variation in tubular reabsorption rather than in glomerular filtration which is responsible for increase in urine volume. In normal subjects polyuria commonly results either from increase in fluid intake or from decrease in sweating. Thus a sudden change from warm to cold weather is commonly associated with a rise in the urine volume, but after a few days of adjustment the urine volume declines as the individual involuntarily diminishes his water intake.

Of the various pathologic states which may be associated with polyuria, diabetes insipidus—a rather rare disease—may be mentioned first, because it gives rise to the largest urine volumes observed in any condition. In this disorder, as the

result of deficiency of the posterior pituitary-hypothalamic regulating mechanism, the tubular reabsorption of water is markedly decreased, and the urine volume may reach the high level of several gallons per day. Such polyuria is apparently brought about by diminished formation of the antidiuretic hormone, consequent to disease of the posterior lobe of the pituitary gland, or to disturbances in the hypothalamic center which regulates its activity. Posterior pituitary extract is, therefore, a specific therapeutic remedy.

In untreated or poorly regulated patients with *diabetes mellitus*, increased urine volume is usually found.

During *recovery from edematous states*, and especially those induced by heart failure, the urine volume may reach large proportions, with corresponding outpouring of sodium and chloride. Diminished tubular reabsorption of water and of electrolytes, rather than increased glomerular filtration, is responsible.

**Renal disease** is a common cause of moderate polyuria. When a large number of nephrons are destroyed, there frequently occurs an increase in the amount of filtration per nephron. The total volume of glomerular filtrate may therefore approach normal. However, the rate of reabsorption per nephron may fail to keep pace with the rate of filtration, and the result is an increased volume of dilute urine. The polyuria eventually tends to give way to diminished volume of dilute urine as the number of functioning glomeruli is cut down still further by the progressive underlying disease process, and as the concentrating power of the remaining tubules declines.

**Oliguria.** Diminished urine volume may occur in normal subjects following a decrease in water intake, or as the result of excessive sweating. Oliguria may likewise result from circulatory disturbances in the kidney, and hence may accompany any of the several types of circulatory failure (Chapter 14). When, as the result of forward failure, the cardiac output per minute is sufficiently diminished, renal vasoconstriction occurs, and the renal blood flow is disproportionately reduced. This compensatory mechanism, which serves to maintain the blood flow to the heart and brain, at the expense of the production of initially reversible renal failure, may, if long maintained, induce irreversible renal failure and the subsequent development of anuria and death.

Aside from disorders in which the renal circulation is affected, as the result of general circulatory disturbance, any local disease process such as nephrosclerosis or glomerulonephritis, which is so advanced as to cause a marked decrease in blood flow through the kidney, may result in oliguria. As has been mentioned, when such disorders are not too far advanced, the oliguria may be preceded by polyuria as the result of deficient tubular reabsorption of the relatively large volume of glomerular filtrate passing from the remaining functional glomeruli. Other primarily renal causes of oliguria include acute glomerulonephritis, poisoning with nephrotoxic substances (such as bichloride of mercury or sulfonamide drugs), rapid and extensive hemolysis following transfusion reactions, and acute cortical necrosis of the kidneys. Among the factors concerned in the production of oliguria in these states are diminished renal blood flow, alterations in the capillary walls of the glomeruli, edema, degeneration and necrosis of the tubular cells, obstruction of tubules by cellular debris and casts, and structural and functional changes in the tubules leading to an increase in passive diffusion of water and solutes back into the blood. The effects of certain precipitating causes of oliguria are markedly exaggerated by concomitant tubular disease. Thus, for example, in the presence of existing tubular degeneration, certain relatively insoluble substances (e.g., hemoglobin and sulfonamide derivatives) may be precipitated and cause a tubular reaction producing tubular blockage, thus further enhancing tubular failure.

One of the commonest causes of oliguria is the rapid accumulation of fluid in the tissues during edema formation. The various mechanisms which may be concerned in edema formation will be discussed in a subsequent chapter. Here, it need only be pointed out that such mechanisms are of two types, those which act in the tissues and those which act in the kidney; and that, of the renal mechanisms, defective excretion of sodium is especially important. The exact means whereby such defective sodium excretion is brought about is a matter of some disagreement at the present time.

When renal tubular function is adequate, oliguria is invariably associated with a high urinary specific gravity. In the terminal stages of chronic renal disease, and occasionally as the result of acute renal disease or of renal functional impairment occurring secondarily to extrarenal disorders, hyposthenuria may occur in the presence of oliguria. Such a combination is of grave prognostic import because it indicates inability of tubules to perform osmotic work under a maximal stimulus.

**Anuria**, or cessation of urine flow, is dependent on the same mechanisms and causes which, when operating less severely, cause oliguria.

**Nocturia** (or nycturia) may be defined as a condition in which an individual has to arise from bed to urinate, prior to the individual's normal time of arising. Normally, during sleep, the urine volume is considerably diminished, and healthy subjects ordinarily do not have to urinate during the sleeping hours. Nocturia is frequently the result of psychogenic disorders which cause disturbed sleep, or which lead to excessive ingestion of water as the result of restlessness. Nocturia may be caused by all of the conditions which produce frequency, and also by those which cause a well-marked increase in urine volume. Hence, it may be conveniently divided into the psychogenic, irritative, and polyuric types.

One of the most important causes of nocturia is inability to excrete a concentrated urine. Normally, the urine decreases in volume during the night, but the amount of total solids excreted per unit of time remains high, this adjustment being brought about as a result of formation of a more concentrated urine. The individual suffering from impairment of renal function loses, at an early stage, the capacity to excrete a concentrated urine, because this capacity depends upon the ability of the kidneys to perform osmotic work. (Such a loss of concentrative power is designated as *hyposthenuria* when of moderate severity, and as *isosthenia* when the osmotic concentration of the urine approaches that of the plasma filtrate.) Hence, the type of nocturia in which the volume of urine during the day is not disturbed, but in which the individual has an increased volume at night, having to get up once or twice to urinate, should immediately lead to the suspicion of renal disease. When, on the other hand, nocturia results from irritative processes in the urinary tract, the nocturnal frequency of urination is apt to be more pronounced. Such patients have to urinate small volumes several times during the normal sleeping period, and therefore differ from subjects with renal disease who urinate larger volumes only once or twice.

## ALTERATIONS IN COMPOSITION OF URINE

In the discussion to follow, only such alterations will be considered as are primarily related to disorders of the urinary system. The numerous chemical disturbances, primarily related to metabolic rather than to renal disorders, are considered elsewhere in the appropriate chapters.

**Proteinuria** is a more suitable term than the commonly used "albuminuria" because serum albumin, while ordinarily the most abundant protein, is not the only protein which may appear in urine. Small quantities of globulin are probably present whenever albuminuria exists in significant degree. The presence of fibrin in the urine indicates either an inflammatory process somewhere in the genitourinary tract, or gross bleeding. Extensive disease of bone marrow, and more particularly multiple myeloma, is frequently associated with the presence of special types of proteins (Bence-Jones proteins) in the urine. However, ordinarily, the chief protein in the urine is serum albumin.

Recent work indicates that glomerular filtrate, like tissue fluid, normally contains a small amount of albumin, but that, in health, this is reabsorbed in the tubules and conserved for the body. The normal urine, therefore, contains either no albumin or only an insignificant amount which is not great enough to give a positive test by the procedures used ordinarily. The appearance of albumin in pathologic amounts in the urine may result from injury to the capillaries of the glomeruli, such as occurs in acute glomerulonephritis, thus increasing the protein content of the glomerular filtrate; from circulatory disturbances, such as occurs in congestive heart failure; from disease of the tubules, with consequent deficiency in reabsorption of protein; or from gross bleeding anywhere in the urinary tract. It should be remembered that many normal people, especially the thin, have small amounts of protein in the urine after remaining in the upright position for a considerable period (orthostatic proteinuria); that protein may appear in the urine of normal subjects following vigorous exercise; and that many febrile conditions are commonly associated with proteinuria. Hence such conditions should be excluded before one draws the conclusion that the presence of protein in the urine is indicative of a significant renal lesion. Some of the impor-

tant points in the differential diagnosis of the more common causes of proteinuria are summarized in table 15.

**Cylindruria**, or the presence of casts in urine, is to be regarded as of pathologic significance only when the number of casts is greater than that which occurs in normal subjects. This decision can be made by a study of a freshly voided overnight specimen according to the technic described by Addis. Since protein furnishes the matrix of the cast, and since the isoelectric point of the blood proteins (i.e., the pH of maximal insolubility) is well on the acid side of neutrality, casts are best seen when the urine is acid. In alkaline urine they may not be demonstrable, as they may dissolve in the bladder. Furthermore, since urine rapidly becomes alkaline on standing, as the result of formation of ammonia from urea by bacterial action, urine to be examined for casts should be studied immediately after being voided. When these precautions are taken, the examination for casts is of importance, because the type of cast gives an indication as to the acuteness and severity of the renal process. Furthermore, the demonstration of casts in a patient with proteinuria constitutes proof that the protein is coming from the kidney and is not getting into the urine at some lower point in the urinary tract as the result of inflammation or bleeding.

Casts may not be demonstrable in dilute urine, for three reasons, namely: (1) excessive dilution; (2) failure of formation; and (3) disintegration.

**Hematuria**, the condition in which red blood cells are present in the urine in abnormal number, is to be distinguished from *hemoglobinuria*. Hemoglobin appears in the urine whenever there is sufficient free hemoglobin in the blood stream to exceed the renal threshold—i.e., the tubular reabsorptive capacity. The most important causes of hemoglobinuria are malaria, transfusion reactions, the hemolytic crises which occur in certain types of anemia, and hemolysis occurring as the result of certain toxic substances such as those contained in snake venom. Hematuria is occasionally the result of renal bleeding consequent to one of the hemorrhagic states (Chapter 23). More commonly, it results from local disorders of the upper and lower urinary tract. The more important points in the differential diagnosis of the commoner causes of hematuria are listed in table 16. It is of special importance to realize that

Table 15  
DIFFERENTIAL DIAGNOSIS OF SOME IMPORTANT CAUSES OF PROTEINURIA

<i>Underlying Cause</i>	<i>Amount of Protein in Urine</i>	<i>Characteristic Casts</i>	<i>Hematuria</i>	<i>Pyuria</i>	<i>Specific Gravity</i>	<i>Blood Urea</i>	<i>Edema</i>	<i>Hypertension</i>	<i>Retinal Changes</i>	<i>Commonly Associated Findings</i>
Acute glomerulonephritis	+++	Cellular	++	+	Normal or high	Normal or elevated	+	+	±	
Nephrotic states*	+++	Fatty or waxy	0	±	Normal	Normal	+++	0 or +	±	Hypo-proteinemia
Benign nephrosclerosis	±	Hyaline and granular	0	0	Normal or low	Normal	0 or cardiac	++	+	Cardiac enlargement
Malignant nephrosclerosis	++	Granular and cellular	+	+	Low	Normal or elevated	0 or cardiac	+++	+++	Rapid progression
Chronic pyelonephritis	+	Hyaline and granular	±	+	Low	Normal or elevated	0 or cardiac	++	+	History of urinary infection
End-stage† kidney	++	Renal failure	±	±	Low	Elevated	0 or cardiac	++	++	
Eclampsia	++	Granular	±	±	Normal	Normal	+	++	++	Pregnancy Convulsions
Congestive heart failure	++	Hyaline Granular	±	0	Normal	Normal	Cardiac	0 or +	0 or +	Dyspnea, edema, cardiac enlargement
Bleeding into urinary tract	+	None	++	±	Normal	Normal	0	0	0	
Orthostatic proteinuria	+	Hyaline	0	0	Normal	Normal	0	0	0	Proteinuria disappears when recumbent

\* Including the nephrotic stage of glomerulonephritis, amyloidosis, syphilitic nephrosis, primary lipoid nephrosis, and intercapillary glomerulosclerosis.

† Failing, contracted kidney secondary to glomerulonephritis, nephrosclerosis or pyelonephritis.

the appearance of blood in the urine of the female cannot be considered as of pathologic significance unless the urine is obtained by catheter.

**Pyuria**, or the appearance of polymorphonuclear leukocytes in urine is likewise to be considered as significant in the female patient only when the specimen of urine has been obtained by catheter. Infections and tumors of the urinary tract constitute the commonest causes.

**Changes in the Colloidal State of Urine (Nephrolithiasis).** The tubular modification of the glomerular filtrate ordinarily results in a urine in which solutes have been concentrated to variable degrees, and the hydrogen-ion concentration either increased or decreased. In consequence, the urine is often supersaturated in respect to several

constituents. Normally, this state of supersaturation is maintained until after the urine has been voided, or at least until it has reached the bladder, so that significant precipitation does not occur. That which does occur results in a finely dispersed sediment which is washed readily from the urinary tract, mechanically. Of those solutes for which the urine of average composition may be supersaturated, the following are the most important:

<i>Solute</i>	<i>Urine Is Supersaturated</i>
Calcium acid phosphate.....	above pH 5.3
Magnesium ammonium phosphate.....	above pH 6.2
Uric acid.....	below pH 6.0
Sodium or ammonium urate....	from pH 4.6 to pH 9.0
Calcium oxalate.....	above pH 4.0

Table 16

## DIFFERENTIAL DIAGNOSIS OF THE MORE IMPORTANT CAUSES OF MACROSCOPIC HEMATURIA

Condition	Proteinuria	Urinary Findings			Clinical Findings			Special Procedures	Remarks
		Casts	Leuko-cytes	Hypertension	Edema	Tend-ency to Uremia	Fre-quency and Dysuria		
Hemorrhagic diseases	+	±	0	0	0	0	±	See Chap. 23	Hemorrhage in skin and elsewhere
Acute glomerulonephritis	+++	Cellular and others	+	+	+	+	±	..	..
Chronic glomerulonephritis	+	Granular and hyaline	±	++	Renal or cardiac	+++	0	Slow decline in renal function	Vascular retinopathy +
Malignant nephrosclerosis	++	Granular and hyaline	+	+++	None or cardiac	+++	0	Progressive decline in renal function	Vascular retinopathy +++
Benign nephrosclerosis	±	±	±	++	0 or cardiac	+	0	..	..
Tumors and infection of kidneys	±	0	++	+	0	++	+	Pyelography	Differential renal function
Nephrolithiasis	±	0	++	±	0	+	++	X-ray Pyelography Cystoscopy	Renal colic
Tumors and infection of bladder	±	0	+++	0	0	0	+++	Cystoscopy	..
Hyperatrophy and carcinoma of prostate	±	0	++	0	0	+++	+++	Cystoscopy	Rectal examination
Contamination (menstruation, etc.)	+	0	+	0	0	0	0	..	Vaginal examination

The mechanisms maintaining such supersaturation are as yet little understood, but probably include the following, among others: (1) Solvent action of urea and certain other urine constituents; (2) protective colloidal properties of traces of proteins—e.g., sulfomucin; and (3) absence of contact with a solid phase to initiate and act as a focus for precipitation. In addition, citrate, or citrate-like substance, in the urine tends to form soluble nonionized complexes with calcium ions, so that actual degree of supersaturation with calcium salts is not so great as could be calculated from total calcium concentration.

It is rather generally agreed that excessive pre-

cipitation may take place with sediment formation, without development of renal concretions or calculi. When these do develop, at least three factors are of fundamental importance: (1) The degree of supersaturation for the solute concerned (and for other solutes, in so far as the presence of the latter affects the solubility of the former). (2) The existence of a focus for initiation of the localized precipitation; i.e., a "pre-calculus lesion." (3) Time for precipitation of the supersaturated solutes at the focus.

The degree of supersaturation for various solutes is in turn related to several circumstances. These include, most importantly, at least, the

following: (1) *The pH of the urine.* This is a function of such variables as the character of the diet, acid-base balance, presence or absence of urinary tract infection with urea-splitting organisms, and presence or absence of normal renal tubular function. (2) *The specific gravity of the urine.* This also is a function of diet and renal tubular function, and, in addition, of water intake and environment (climate). (3) *Presence of certain metabolic disorders* leading to excessive concentrations of certain solutes in urine; e.g., hyperparathyroidism, cystinuria, xanthuria, gout, and negative calcium and phosphorus balances concomitant with or following trauma, infection with fever, wasting diseases, or even prolonged bed rest. In addition, diminution in citrate excretion may be a contributing factor to supersaturation in respect to calcium salts.

An increased excretion of oxalic acid in the urine, known as oxaluria, may occur in states of gastric hyperacidity in which the absorption of oxalic acid is increased, or in digestive disorders where an increased breakdown of carbohydrate to oxalic acid occurs in the intestinal tract. Oxaluria may produce symptoms either by irritation of the lower urinary tract caused by the crystals themselves or by the formation of oxalate stones. Essential phosphaturia (phosphatic diabetes) may be caused by worry, loss of sleep, or a heavy protein meal, and is seen occasionally in association with gastric or duodenal ulcers. In the latter instance it is probably the result of excessive ingestion of milk and alkali. Phosphaturia, like oxaluria, may produce symptoms by the irritation of crystals in the lower urinary tract or by the formation of phosphate stones. These conditions both may be relieved by correcting the conditions leading to them. In addition, the use of aluminum hydroxide to precipitate phosphate as an insoluble aluminum phosphate in the intestinal tract, thus preventing its absorption, is a valuable procedure in the treatment of essential phosphaturia.

Foci for the initiation and perpetuation of precipitation may be provided in a number of ways. Focal injury of any sort may produce clumps of blood, albumin, and fibrin, which act as nuclei. Infection, with localized injury to tissues constituting the lining of the upper urinary passages, may provide the focus, or result in the production of blood clots, clumps or organisms, albumin, or fibrin, which in turn are foci. In certain experi-

mental animals, localized lesions of the urinary tract epithelium may be produced under conditions of vitamin A deficiency, and these act as initiating foci. In man, minute subepithelial depositions of calcium phosphate in the renal papillae (Randall's plaques) are thought often to constitute precalculous lesions, which, after undergoing necrosis at the epithelial surface, become foci for deposition.

Time for excessive precipitation upon foci is provided by those circumstances leading to stasis of urine in the pelvic channels. These include obstruction from any cause, presence of hereditary anomalies interfering with the gravity flow of urine, and position—as, for example, in the relatively immobilized bedridden patient.

Bacterial infection favors nephrolithiasis through at least two different mechanisms, one being alteration of the pH of the urine, and the second being the provision of a protein nucleus upon which organic or inorganic substances may precipitate.

It follows, from these considerations, that much may be done to minimize the initiation and rate of development of renal calculi by procedures designed to decrease the degree of supersaturation, to eliminate foci for precipitation, and to combat stasis. In this respect it should be emphasized that exact knowledge of the qualitative chemical composition of any previous concretion a patient may have developed is obligatory, in order, rationally, to devise subsequent preventive measures. Thus the demonstration that an individual has stones composed primarily of urates constitutes an indication for alkali therapy, since urates are more soluble in alkaline than in acid solution. Similarly, the finding of phosphate calculi should direct attention toward the possibilities of stasis, infection, or primary disturbances in mineral metabolism. Some of the more pertinent points in regard to the various types of renal concretions are summarized in table 17.

#### UREMIA

Although this term was originally used to mean excess of urea in the blood, it is now applied in a wider sense, and refers to a clinical syndrome resulting from the failure of excretion of waste products, and the failure of conservation of needed substances, consequent to primary disorders of the kidney. When defined in this

Table 17

SUMMARY OF SOME OF THE IMPORTANT FEATURES OF THE MOST FREQUENTLY ENCOUNTERED RENAL CALCULI

<i>Types of Calculi*</i>	<i>Relative Frequency</i>	<i>Urine pH Favoring Formation</i>	<i>Remarks</i>
Phosphate (mixed amorphous)	Common	Alkaline	These are almost invariably mixed stones, with calcium oxalate, calcium carbonate, and alkali urates as the chief lesser components. Metabolic origin (e.g., hyperparathyroidism) must be considered
Phosphate (magnesium phosphate)	Common	Alkaline	
Phosphate (calcium or calcium and magnesium phosphate)	Common	Alkaline	
Calcium oxalate	Common	Alkaline or acid	Rather rare as "pure" stones
Calcium carbonate	Very rare	Alkaline	Not uncommon as a lesser component of mixed stones
Uric acid	Common	Acid; urates also form in alkaline urine	Rather rare as "pure" stones; nonopaque to x-ray unless other opaque components are present in sufficient quantity
Cysteine	Rather rare	Acid	Usually present as "pure" stones; tendency is familial; nonopaque to x-ray
Xanthine	Rare	Acid	Frequently occurs as "pure" stones; nonopaque to x-ray

\* These stones are classified according to the predominant component they contain. The majority of calculi are mixed in composition.

manner it must be sharply distinguished from the condition formerly called "pseudourmia," and now spoken of as "hypertensive encephalopathy" or "cerebral vascular crisis." The latter state is closely related to cerebral vascular disorders and edema of the brain. It is of two overlapping types, of which one is the acute "pseudourmia" commonly observed in patients with acute nephritis and with eclampsia. Its distinguishing hallmarks are a rising blood pressure, headache, vomiting, visual disturbances, papilledema, progressive coma, and convulsions; and there is much evidence that the state is closely related not only to circulatory disturbances, but also to disturbances similar to "water intoxication" (Chapter 28). The term "chronic pseudourmia" has been applied to those disturbances of consciousness, or of motor or sensory function, which occur in persons with chronic severe hypertension, and which last only a few minutes to a few hours. Prior to the modern methods of chemical examination of the blood, both of these types of hypertensive encephalopathy, which frequently but not necessarily occur in patients with

true renal failure, were confused with uremia. However, it is now known that they are not dependent on failure of renal excretory function, but on the vascular disease, and on the disturbance in fluid balance which commonly, but not necessarily, accompanies renal failure.

Uremia due to primary renal disease must likewise be distinguished from other conditions in which chemical changes in the blood similar to those of uremia occur as the result not of primary renal disease but of disturbances in the circulation, in the fluid balance, or in the metabolism, arising elsewhere in the body.

Elevation of nitrogenous constituents of the blood due to such causes is often termed "prerenal azotemia." Although this term is in the strict sense a misnomer, the concept is useful in that it tends to distinguish the azotemia of primary renal origin from that which is only secondarily of renal origin. The common causes of prerenal azotemia are acute circulatory failure (Chapter 14), inadequacy of fluid intake, bleeding into the upper small intestine, and excessive loss of fluid and electrolytes as the result of

vomiting, diarrhea, etc. In patients with prerenal azotemia the blood urea is elevated, but the clinical picture is dominated by the primary disease process, which may be in the heart, the central nervous system, the peripheral circulatory apparatus, or the gastrointestinal tract. Furthermore, in true uremia resulting from chronic renal disease, the concentrating power of the kidney is lost, and the specific gravity of the urine approaches that of an ultrafiltrate of blood plasma —i.e., about 1.010. In the initial phases of prerenal azotemia the specific gravity of the urine is usually elevated, but, if the circulatory disturbance in the kidney lasts long enough, prerenal azotemia may be complicated by true uremia resulting from renal failure consequent to the alteration in renal blood flow, and the specific gravity then declines. Aside from disorders of the circulatory system, intestinal obstruction, with copious vomiting, is perhaps the most common cause of prerenal azotemia.

In the production of the manifestations of uremia, two factors are particularly concerned. One of these is *excess* of certain substances, of which the various nitrogen-containing components of the urine, the phenolic bodies, phosphates, potassium, water, and acidic ions are perhaps the most important. The other is *deficiency* of certain substances. Such deficiencies arise secondarily, as the result either of retention of chemical antagonists, or of loss by the kidney or other routes. Thus retention of nonvolatile acids, defective ammonia formation, and failure to conserve sodium all tend to cause deficiency of bicarbonate; retention of phosphate causes deficiency of calcium, while the polyuria which commonly precedes renal failure, plus the anorexia and vomiting which usually accompany it, lead to deficit of water, sodium, and chloride. Since it is easier to remedy a deficit than to overcome an excess, a search for deficiencies of essential components of the body fluids is of special practical importance in patients suffering from uremia.

**Clinical Manifestations.** The clinical manifestations of uremia are protean. In the discussion to follow an attempt will be made to explain the mechanism of some of the more important of these manifestations. However, it should be borne in mind that there are probably many un-

known metabolites which are retained, and that knowledge of the chemical disturbances is still scanty. Hence, the discussion to follow should be regarded as tentative, and as representing only a summary of a subject about which knowledge is decidedly incomplete.

**SKIN.** The skin often displays a peculiar discoloration, being a brownish muddy gray (*café au lait*). This is particularly marked in the hands and face, while the remaining skin may be normal in color, or display only pallor. The discoloration is probably to be ascribed to the oxidation of urochromogen to urochrome in those parts of the skin exposed to light. This pigment, urochrome, normally gives the characteristic yellow color to urine.

Eruptions of various types are commonly observed in uremic patients as the result of unknown causes, or of defective renal excretion of administered drugs. Purpuric manifestations are likewise observed frequently, and extensive ecchymosis is not uncommon. The mechanism of this hemorrhagic state in uremia has never been clearly elucidated.

**NERVOUS SYSTEM.** The nervous system is affected profoundly by the uremic state. Manifestations of both irritation and depression occur. The former consist of muscular twitchings and, in the terminal phase, of convulsions. The patients are frequently sleepy or "dopey," and tend to drowse but do not sleep soundly. This state of sleepiness, in which the mental faculties are clear when the subject is aroused, gradually gives way to a confused stupor which eventually terminates in profound coma.

The chemical changes responsible for these disturbances in the nervous system are not completely known, but it is probable that deficiency of ionized calcium as the result of the retention of phosphate (and possibly of oxalate and citrate), and also as the result of retention of potassium and guanidine, which are physiologic antagonists of calcium, is a major factor in the causation of the twitchings and the convulsions. The stupor and coma are probably related to a number of alterations, the generalized "dehydration" and the retention of phenolic compounds being among the more important factors. Thus, in a given patient, either the irritative phenomena or the manifestations of depression

may predominate, depending on the balance of these and unknown factors.

**RESPIRATORY SYSTEM.** Respiratory disturbances are common in uremic patients. The older subjects frequently display Cheyne-Stokes respiration, which probably results from the combination of deficient cerebral blood flow and depression of the respiratory center as the result of the intoxicative state. When increased intracranial pressure exists, slow stertorous breathing is common. Outspoken acidosis may be accompanied by the characteristic Kussmaul breathing, with deep sighing respirations and only slight elevation of the rate. When heart failure coexists, the respiration is rapid and labored, with a panting quality. Any combination of these respiratory disturbances may occur in patients who have uremia.

**CIRCULATORY APPARATUS.** Aside from congestive heart failure, the outspoken changes commonly found in the circulatory apparatus of uremic subjects are hypertension, vascular retinopathy, and pericarditis. *Hypertension* is not an invariable accompaniment of uremia. It is commonly absent when the uremic state is induced by acute cortical necrosis of the kidneys, or by intoxication with bichloride of mercury. A goodly percentage of the patients with uremia secondary to renal tuberculosis, or to amyloid disease, fail to show hypertension. However, the rise in blood pressure is present in the great majority of the cases.

*Vascular retinopathy* is commonly absent in those patients who display no hypertension. This change is not directly related to the uremic state, but since a general parallelism exists between the severity of vascular lesions in the kidney and those in the retina, any patient with well-marked hemorrhage and exudate, plus vascular changes, who does not have uremia, should be regarded as a likely candidate for it. The concept that there is a specific "uremic retinopathy" does not appear to be sound.

*Pericarditis* is a frequent finding in uremia, and is painless in the vast majority of instances. An occasional patient, however, may have severe pain with this condition, and may thereby be falsely considered to have myocardial infarction or dissecting aneurysm. The mechanism of the pericarditis is unknown.

*Cardiac disorders* are commonly observed in uremic patients, and one of the possible mechanisms is alteration of the ratio between potassium and calcium. Since the former substance is usually elevated in uremic patients and the latter depressed, a well-marked alteration in the ionic balance may occur; and since such an alteration produces disorders of the rhythm in experimental animals, it affords a likely explanation for such disturbances in uremic patients. Potassium excess, either absolute or relative to calcium, is also thought to be a factor in the production of the pronounced alterations in the configuration of the electrocardiogram which are commonly observed.

**GASTROINTESTINAL DISTURBANCES.** Striking disturbances in the gastrointestinal functions are usually present. *Anorexia, nausea, and vomiting* are among the earliest symptoms to appear, are frequently intractable, and commonly cause more discomfort than all of the other manifestations combined. The cause of these symptoms is probably not uniform, but among the factors concerned are elevation of intracranial pressure, intoxication by administered drugs as the result of impaired excretion, and local irritation throughout the gastrointestinal tract consequent to the formation by bacterial action of the highly irritating ammonium ion from the large amount of urea present in the gut. Possibly, guanidine retention also plays a role in production of the gastrointestinal symptoms.

*Bleeding from the stomach or rectum* is not uncommon in uremic subjects, and, since such patients frequently also have vomiting or diarrhea, they are often incorrectly considered to be suffering from neoplastic disease of the stomach or large bowel. In such uremic patients the small and large intestines are frequently the sites of purpuric ecchymoses, which may proceed to necrosis and ulceration.

The decision as to the nature of the underlying process responsible for uremia is often a difficult one if the patient is seen only in the terminal phase. The chief difficulty arises from the fact that the clinical pictures of three conditions commonly responsible for uremia—nephrosclerosis, glomerulonephritis, and chronic pyelonephritis—while different in the early stages, may become almost identical in the terminal stage of the proc-

ess. From a practical standpoint it is especially important that uremia due to these causes, which is essentially resistant to treatment, be differentiated from uremia resulting from obstructive conditions of the urinary tract, and from functional renal insufficiency (prerenal azotemia), the cause of which is frequently amenable to therapy. Some important points in the differential diagnosis of some of the more common causes of uremia are summarized in tables 15 and 16.

**Treatment.** The most important general principles which should be considered in relation to the treatment of uremia are as follows:

1. The determination as to whether the uremic state is due to a curable condition. In this regard, one should first look for circulatory and abdominal disorders (such as vomiting due to intestinal obstruction), and then for obstructive conditions of the urinary tract capable of alleviation by surgical treatment. One should then attempt to decide, on the basis of the history and the urinary findings, whether the uremia is due to a solely chronic process, to an acute renal disorder, or to an acute exacerbation of a chronic renal disorder. In so far as the uremia is related to congestion, edema, and other disorders which may be remedied by time, a great deal can be expected from treatment. On the other hand, in so far as the uremia is due to scar tissue in the renal blood vessels and the glomeruli, treatment will necessarily be unavailing. Further attention should be given to the possibility that the uremic state has been induced by faulty transfusions, administration of sulfonamide drugs, etc. In case such a suspicion exists, alkalinization of the urine may be a valuable procedure. Even when all the evidence points toward chronic renal disease, one should be satisfied that congestion of the kidney as the result of heart failure has not been an additional precipitating factor, because this condition can commonly be reversed by treatment.

2. A second principle is that of overcoming deficits in vital body components. For this purpose one seeks for and remedies evidence of calcium ion deficiency, bicarbonate deficiency, and deprivation of water, sodium, and chloride (Chapters 28, 29).

3. Attempts to overcome excesses. This is a difficult procedure. Experience has demonstrated the inadequacy of the procedures of venesection and diaphoresis, as commonly employed in the

past. The use of an indwelling tube in the stomach or duodenum, discarding the secretions so obtained and restoring sodium, chloride, and water, is often employed, but is only slightly effective. A more difficult but more effective method occasionally used consists of the procedure of peritoneal dialysis. For this purpose large amounts of a modified Tyrode's solution are injected into the peritoneal cavity and removed either by a second needle placed simultaneously in another part of the peritoneum, or by a subsequent paracentesis. The procedure is less hazardous than formerly, in view of the availability of modern antibiotics, but merits further experimental trial before being widely adopted for clinical use.

Very recently, the principle of the "artificial kidney," used formerly in animal experiments, has been applied to man. The method consists of passing the blood of the uremic patient through a dialyzing apparatus. Although, at the present time, the procedure is to be regarded as experimental, the principle is sound, and it can be anticipated that the method will be applied widely when the technical difficulties have been overcome. Granting that no lasting benefit can be expected when the excretory failure is the result of chronic disease, with extensive renal scarring, the fact remains that such utilization of the dialyzing method may prove life-saving in individuals with severe renal failure due to acute but reversible injury (e.g., transfusion of incompatible blood, sulfonamide intoxication, the crush syndrome, acute nephritis, etc.).

4. The final principle involved in the management of uremia is the attempt to spare the kidney, and at the same time to afford adequate nourishment of the body. A diet low in protein is desirable, from the standpoint both of diminished renal load and of reduction in aromatic amino acids, which are important precursors of the highly toxic phenolic substances.

The treatment of uremia due to chronic primary renal disease is, in general, discouraging. One occasionally encounters a dramatically beneficial result, particularly when an element of obstruction, infection, congestion, or acute exacerbation coexists. Since one cannot always predict with certainty which patients have such components, it is justifiable to treat all patients intensively along the lines which have been described.

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## 20

### Edema

C. A. Moyer and T. R. Harrison

#### Pathogenesis of Edema

- Tissue Factors in Edema Formation
- Renal Factors in Edema Formation
- Differential Diagnosis of Edema

Strictly speaking, the term "edema" refers to an increased amount of fluid in the tissues, whether the excess be inside or outside the individual cells. From the standpoint of clinical medicine, it is the increase in extracellular fluid in the subcutaneous tissues and in the body cavities which is of special importance. The term "edema," therefore, usually refers to a recognizable increase in the amount of fluid in the subcutaneous tissues, and is synonymous with the older term, "dropsy." "Ascites" and "hydrothorax" refer to the presence of free fluid in the peritoneal and pleural cavities, respectively, while "anasarca" indicates the accumulation of excess fluid in all of these several regions.

When edema is of considerable degree it may be recognized by "pitting" of the tissues—e.g., by the persistence of an indentation of the skin following pressure against a bony eminence, usually the lower tibia. However, since edema fluid is widely distributed, there may be an excess of several liters in the volume of the extracellular fluid before pitting can be demonstrated. There-

fore, a rapid gain in weight is the earliest indication of generalized edema formation.

#### PATHOGENESIS OF EDEMA

In order for generalized edema of significant degree to develop, two conditions must be fulfilled: (1) The rate at which fluid enters the tissues from the blood stream must exceed the rate at which fluid leaves the tissues. (2) The fluid output of the body must be less than the fluid intake. We therefore must think of tissue factors and of renal factors. The former are now fairly well understood; the latter, although considerably elucidated by the work of the past few years, remain obscure in certain respects.

The tissue factors determine where edema will occur, and it is possible for the tissue factors alone to lead to the development of edema in limited areas, the local increase in extracellular fluid volume being purchased at the price of a decline in the extracellular fluid content of the remaining nonedematous parts. However, such a process can be limited only in degree, for any significant decline in extracellular fluid volume of a large portion of the body leads, through mechanisms as yet poorly understood, to retention of

sodium and water by the kidney. Hence the renal factor is important in all types of generalized edema, and constitutes the quantitative determinant as well as the common denominator of edema formation, while tissue factors constitute the qualitative determinant, and vary according to the specific mechanism concerned.

The most important mechanisms concerned in edema formation may be summarized as follows:

I. Tissue factors:

- A. Increased capillary blood pressure:
    - 1. Arteriolar dilatation (e.g., inflammation)
    - 2. Increased venous pressure:
      - a. Local (e.g., venous obstruction)
      - b. General (e.g., congestive heart failure)
  - B. Diminished colloid osmotic pressure of blood (hypoproteinemia):
    - 1. Deficient protein intake (certain types of nutritional edema)
    - 2. Disordered protein formation (hepatic disease)
    - 3. Excessive loss of protein (e.g., nephrotic states)
  - C. Increased capillary permeability (e.g., inflammation)
  - D. Increased colloid osmotic pressure in tissues (inflammation)
  - E. Decreased mechanical pressure in tissues (usually important only in determining where edema occurs rather than whether it occurs)
  - F. Interference with lymph drainage (e.g., chronic lymphangitis)
  - G. Unknown mechanisms (e.g., Milroy's disease: certain types of nutritional edema)
- II. Renal factors: Decreased glomerular filtration and/or increased tubular reabsorption of sodium and, secondarily, of water, as the result of poorly understood mechanisms. (Probably the primary mechanism in acute glomerulonephritis and certain endocrine disorders, and an important secondary mechanism in all types of edema.)

#### TISSUE FACTORS IN EDEMA FORMATION

1. Increase in Capillary Blood Pressure. Such a change may be brought about as the result of

either: (a) *dilatation of the arterioles*, such as occurs, for example, when the hand is placed in hot water, and which is associated with flushing of the skin; or (b) *increase in venous pressure*, which may be either local, as the result of venous obstruction, or general, as in congestive heart failure, and which is often associated with cyanosis.

Aside from congestive heart failure, the general venous pressure may be elevated when there is rapid retention of sodium in the body, either as the result of acute nephritis, or following the ingestion of excessive amounts of sodium chloride.

It was formerly believed that increase in venous pressure per se could cause well-marked edema. However, the demonstration that only minimal edema may occur following ligation of the inferior vena cava, despite striking elevation of venous pressure, indicates that this concept must be revised. Apparently the lymphatic vessels may function as important collateral channels for the escape of excess fluid from the tissues when the venous pressure is elevated (Chapter 14).

**2. Diminution in Colloid Osmotic Pressure of the Blood.** Since the capillary wall is readily permeable to small molecules such as glucose, urea, and electrolytes, the concentration of such substances is approximately the same in the blood and in the extracellular fluids, and hence they exert no differential osmotic effect. The situation is quite different with regard to the large protein molecules, which do not pass readily through the capillary walls, and which, therefore, exert an attractive force (the colloid osmotic pressure) which tends to draw water into the blood. Under ordinary conditions this force, tending to pull water in from the tissues, is neatly balanced by the opposite force—the intracapillary pressure—which tends to push water out into the tissues, the mechanical and osmotic effects predominating at the arterial and venous ends of the capillaries, respectively.

The colloid osmotic pressure may be diminished by any condition which leads to a reduction of the plasma protein—more particularly, of the albumin—which, being a smaller molecule than the globulin, has a correspondingly greater osmotic activity per unit mass, 1 Gm. of albumin being osmotically equivalent to about 4 Gm. of globulin. Among the more common mechanisms which lead to a reduction of the proteins are the following: (1) *diminished formation* as the result

of: (a) *deficient protein intake* (example: nutritional edema), or (b) *disease of the liver* (example: cirrhosis); and (2) *excessive loss* (example: nephrotic states).

**3. Increased permeability of the capillary walls** to protein may be brought about by injury as the result of chemical, bacterial, thermal, or mechanical agents, and is an important factor in the production of inflammatory edema, which may readily be recognized by the presence of the other signs of inflammation—i.e., redness, heat, and tenderness. As protein escapes into the tissues, the normal osmotic gradient is reduced and edema tends to result. When edema is due to increased capillary permeability, the tissue fluid partakes of the character of an exudate and has an abnormally high protein content. When capillary damage is severe and widespread, such as may occur, for example, in patients with Rocky Mountain spotted fever, the amount of protein escaping into the tissues may be sufficiently great to produce hypoproteinemia, which increases further the tendency toward edema formation.

Krogh showed that, even in the absence of inflammation and injury, simple dilatation of the capillaries favors edema formation. When other factors (such as the mechanical and colloid osmotic pressures) remain the same, the increase in filtering surface as the result of dilatation will favor the passage of fluid through the capillary walls. Theoretically, the increased rate of movement might be expected to operate equally in both directions, but actually the dilatation of capillaries favors outward movement more than inward. The reasons for this discrepancy are not clear but the fact remains that capillary dilatation tends to produce edema.

**4. Interference with the flow of lymph** likewise tends to produce edema. The swelling of the arm which occasionally complicates extensive operative procedures in the axilla, the extreme edema of the legs in persons with elephantiasis secondary to filarial infections, and the edema of an extremity following recurrent attacks of lymphangitis constitute important examples. In patients with congestive heart failure the drainage of lymph may be impaired as the result of the increase in systemic venous pressure, and this gravity factor is particularly important in the lower part of the body when, as is usually the case, the coexistence of dyspnea forces the patient to assume the sitting posture for long pe-

riods of time. Hence increase in venous pressure not only tends to cause more fluid to pass into the tissues from the capillaries, but also may interfere with the passage of fluid out of the tissues by way of the lymph channels. Since arterial pulsation is an important factor in lymph flow, disorders which cause reduction of pulse pressure tend to favor edema formation. This factor may be of special significance in relation to the visceral edema which tends to occur in the terminal stages of peripheral circulatory failure. It may also be of importance in certain patients with heart failure and decline in blood pressure. However, since patients with aortic insufficiency and marked elevation of pulse pressure often have outspoken edema, it is evident that this factor does not necessarily play a major role in edema formation.

**5. The mechanical pressure in the tissues** is a factor of little or no primary importance in the causation of edema, but is of considerable secondary significance in that, when other things are equal, edema tends to occur most readily either in those tissues, such as the eyelids, in which the tissue tension is normally least, or in tissues which have lost their elasticity as the result of stretching by previous edema, or for other reasons.

**6. The osmotic pressure in the tissues** is of little significance in noninflammatory edema, but when inflammation exists the increase in capillary permeability may allow sufficient protein to escape to produce a significant increase in the local osmotic pressure, which tends to hold the water in the tissues.

#### RENAL FACTORS IN EDEMA FORMATION

The foregoing discussion explains why fluid tends to accumulate in local areas. However, if we think of the patient as a whole, it is obvious that no considerable amount of edema can accumulate unless the intake of fluid exceeds the loss from the body. On first thought, one might consider that the amount of water ingested would be the determining factor. Such, however, is not the case. Any excess of water is distributed between the extracellular and intracellular tissue fluids and, in those exceptional circumstances associated with water excess (Chapter 28), severe symptoms occur before there is opportunity for sufficient increase in extracellular fluid volume to

produce edema. When, on the other hand, there is an excess of both water and sodium, only a small proportion of the sodium diffuses into the cells, and osmotic forces keep the water in the extracellular spaces. Furthermore, the sodium concentration of the extracellular fluids is one of the most jealously guarded constants of the body and tends to be maintained at a constant level, even at the expense of marked alterations in the volume of the body fluids. Thus, under all ordinary circumstances, the kidney responds by diuresis to any increase in water intake, unless this is accompanied by a corresponding increase in sodium intake. The normal kidney may increase its water output twentyfold (i.e., 20 liters, or more, per day), but the reserve is much lower as regards sodium, an intake of as little as three times the normal average of 3 to 6 Gm. per day tending to produce edema. Ordinarily, then, water will be retained only when sodium is also being retained.

The mechanism whereby the kidney retains sodium has been studied extensively. In the case of congestive heart failure it has been demonstrated that the rates of renal blood flow and of glomerular filtration are reduced, but that reabsorption of sodium proceeds at a relatively normal level, and the hypothesis has been advanced that the reduction in renal blood flow is the fundamental cause of sodium retention and edema. Among the objections to this idea are the facts that patients with advanced nephrosclerosis and marked decline in renal blood flow are not edematous, and that drastic reduction of renal blood flow in an animal by partial occlusion of the renal arteries does not lead to edema. (The point has been made that under such conditions the tubules may be deranged and unable to reabsorb sodium. However, such cannot be the case in patients with malignant nephrosclerosis who may develop marked edema and sodium retention when congestive failure supervenes.)

There is likewise evidence that sodium depletion (which occurs in most patients with congestive failure under the modern plan of therapy) may reduce glomerular filtration, and it is uncertain whether diminished filtration of sodium is mainly the result of the disease or of its management.

It has been shown that elevation of renal venous pressure may cause the kidney to retain so-

dium, even though the rate of glomerular filtration remains unchanged. On the other hand, in patients with congestive failure there is no parallelism between the height of venous pressure and the tendency to retain sodium. Furthermore, patients with peripheral circulatory failure and diminished venous pressure display marked sodium retention.

Alterations in hemodynamics in the head appear capable of affecting sodium output. Thus the urinary excretion of sodium is ordinarily less in the sitting than in the recumbent posture. However, compression of the neck of the sitting subject causes the sodium output to approach that in the recumbent position. Administration of hypertonic albumin solution causes decline in sodium excretion. These facts, taken together, suggest that deficit of extracellular fluid in the cranial cavity tends, through some unknown mechanism, to cause the kidney to retain sodium. It would appear, therefore, that the orthopneic patient tends to accumulate edema not only because of the gravitational increase in hydrostatic pressure in the legs, but apparently also because of sodium retention consequent to diminished hydrostatic pressure in the head.

The capacity of the kidney to retain or excrete sodium is remarkably influenced by certain steroid substances of endocrine origin, and, since the total amount of water in the body tends to vary in direct proportion to the total amount of sodium, alterations of steroid metabolism tend to be reflected by changes in the volume of the tissue fluid. Premenstrual edema, the generalized edema which often occurs in normal pregnant women, and the dehydration of Addison's disease, are examples of this important mechanism.

It has been shown that the sodium content of the sweat is diminished in certain patients with congestive heart failure, and this constitutes strong evidence that hyperfunction of the adrenal glands may play a role in the production of edema.

It has been suggested that sodium retention may be the result of decline in cardiac output in relation to body needs. However, if this were true, one would expect to find sodium retention and edema in patients with outspoken arterial anoxia and in normal subjects given digitalis, which causes decline in cardiac output in such individuals. The absence of edema under such

circumstances constitutes evidence against this hypothesis.

Another important factor in the retention of sodium in many patients is sodium depletion as the result of long-standing dietary restriction and the repeated administration of diuretic drugs. Such depletion tends to cause decline in glomerular filtration and also increase in tubular reabsorption of sodium.

The foregoing paragraphs may be summarized as follows: The mechanism of sodium retention in edematous patients is not yet clear. Apparently diminished filtration is less important than increased reabsorption, but the relative importance of the various factors favoring increased reabsorption remains uncertain.

The concept, already mentioned, that retention of water is entirely secondary to that of sodium does not appear to be correct. It is true that the majority of patients with edema may ingest water freely without increase in edema. However, such subjects usually are already suffering from depletion of sodium stores, and ingestion of water readily leads to decreased osmolar concentration with consequent diuresis. Furthermore, it was shown more than two decades ago that the diuretic response of edematous patients to water drinking is less prompt and complete than in the case of normal subjects. Finally, there is strong evidence of the existence of an excess of an antidiuretic substance in the body fluids of certain edematous patients. More evidence is needed before final conclusions can be drawn concerning the relative importance and primacy of retention of water and of sodium.

The renal factors in edema formation are not only those of retention of sodium and of water. Potassium exchange is also important because this cation, being chiefly intracellular, has an important influence in the distribution of water between the intracellular and extracellular compartments (Chapter 29). Furthermore, the availability of different anions is also a factor. Thus administration of sodium chloride tends to cause retention of water, but other sodium salts such as the citrate or succinate may have the opposite effect. Conversely, a diuretic effect may be observed when chloride is administered as the ammonium or potassium salt. It is apparent that edema formation is related not only to retention

of water and of sodium, but also to retention of chloride and possibly of other electrolytes.

Excessive intake of sodium chloride by healthy subjects leads to a rise in venous pressure which may be followed by slight edema. Apparently, the rise in venous pressure which occurs in patients with acute nephritis, even in the absence of heart failure, is due to hydremia as the result of sodium chloride retention. Whether, in this condition, the rise in venous pressure is the only tissue factor concerned remains uncertain. The idea that the edema of acute glomerulonephritis is dependent on generalized capillary injury, with consequent increase in capillary permeability, cannot be regarded as valid, in view of the demonstration that edema fluid has a low content of protein. It seems clear that, in patients with congestive heart failure, sodium chloride retention as the result of alterations in renal function causes further elevation of venous and lymphatic pressures, and thereby aggravates the tendency toward edema formation. Until more is known concerning the mechanisms which influence electrolyte retention by the kidney, the exact role of this organ in the pathogenesis of anasarca must remain obscure. However, the importance of the renal factor cannot be questioned.

#### DIFFERENTIAL DIAGNOSIS OF EDEMA

Although the various factors and mechanisms concerned in edema formation are rather complex, the great majority of patients with noninflammatory generalized edema of significant degree will be found to be suffering from either *cardiac, renal, hepatic, or nutritional disorders*. Consequently, the most important procedures in the differential diagnosis of edema are those which will exclude or implicate these several conditions.

The following considerations will suffice to differentiate the common causes of generalized edema in the great majority of instances.

- I. *Cardiac Edema:* Evidence of cardiac disease (enlargement, diastolic murmurs, gallop rhythm, etc.) plus evidence of *cardiac failure*, such as dyspnea, basilar rales, diminished vital capacity, prolonged circulation time, venous distention, *increased venous pressure*, enlargement of liver, etc. (Chapter 14).

**II. Renal Edema:**

- A. Acute glomerulonephritis: Hematuria, proteinuria, hypertension, short duration of edema.
- B. Nephrotic states (including subacute stage of glomerulonephritis, lipid nephrosis, renal amyloidosis, intracapillary glomerulosclerosis, etc.): *Massive proteinuria* with little or no hematuria, fatty or waxy casts, long duration of edema, *hypoproteinemia*, hypercholesterolemia.

**III. Hepatic Edema:** Evidence of cirrhosis or other disease of the liver (collateral venous channels, enlargement, ascites, jaundice, etc.), plus evidence of hepatic dysfunction (*hypoproteinemia*, positive cephalin-cholesterol flocculation, etc.).

**IV. Nutritional Edema:** History of prolonged inadequacy of diet, with or without hypoproteinemia, often accompanied by objective signs, malnutrition, pellagra, etc.

Aside from the findings which have been mentioned, there are certain other points which are often helpful in eliciting the cause of edema.

The *distribution of edema* is often a rough guide to the cause. Thus edema of one leg, one arm, or both arms, usually is due to some condition causing obstruction to vascular or lymphatic channels. Edema associated with hypoproteinemia is likely to be especially marked in the eyelids and face, and to be most pronounced in the morning because of the recumbent posture during the night, while the edema associated with heart failure is commonly more striking in the legs, and in the evening. In the rare types of cardiac disease, such as tricuspid stenosis and constrictive pericarditis, in which orthopnea is absent and the patient prefers the recumbent posture, the gravity factor is equalized and facial edema is common. Less common causes of facial edema include trichinosis, myxedema, and allergic reactions. Edema confined to one side of the body may occur as the result of cerebral lesions affecting the vasmotor fibers on one side of the body.

The *color, thickness, and sensitivity of the skin* are important. Edema associated with local redness, but without tenderness, is likely to be due to simple arteriolar dilatation, but when local

tenderness and increase in temperature coexist, inflammation is likely. Edema associated with local cyanosis only is likely to be due to venous obstruction; edema associated with general but usually slight cyanosis is likely to be due to congestive heart failure. Thickening of the skin in the edematous region suggests chronic inflammation, lymphatic obstruction, or long-standing congestive failure. Soft edema (due to thinness of the skin) associated with pallor ("alabaster facies") suggests hypoproteinemia.

The *venous pressure* is of great importance in evaluating edema. Elevation of this function in one part of the body only suggests venous obstruction. Generalized elevation of venous pressure is almost pathognomonic of congestive heart failure, although it may also occur in patients with acute nephritis, and in normal subjects following the ingestion of large quantities of salt.

Ordinarily, general increase in venous pressure can be recognized by the level at which the cervical veins collapse, but in doubtful cases the venous pressure should be measured.

*Determination of the plasma proteins*, and especially the albumin fraction, is a valuable procedure in the recognition of edema due to diminished colloid osmotic pressure. In the absence of infectious or hepatic disease, measurement of the total protein will suffice, but in doubtful cases the albumin fraction likewise should be measured.

The *amount of albumin in the urine*, while less important as a guide to the cause of edema than that in the blood, may nevertheless afford useful clues. Thus the complete absence of albumin from the urine speaks against both cardiac and renal edema. Slight to moderate albuminuria is the rule in patients with cardiac edema, while persistent massive proteinuria is likely to indicate a primary renal disorder as the cause of edema.

Aside from the points mentioned, which bear directly on the question of the types of edema, much valuable indirect information is obtained from the other features of the examination: the presence or absence of heart disease and of the signs of cardiac failure (Chapter 14); the character of the urinary sediment; the dietary story in relation to protein intake and in relation to foods causing localized edema of the skin (urticaria) or subcutaneous tissues (angioneurotic edema); these points may be invaluable in determining the cause of edema in a given patient.

*To summarize:* When edema is limited to a local area, one should seek particularly for evidence of inflammation, of allergy, or of obstruction to veins or lymphatics. When edema is either generalized, or limited to areas particularly susceptible because of dependency (legs, back) or laxness of the skin (eyelids), one should search especially for evidence of cardiac, renal, or hepatic disease, or for manifestations of nutritional deficiency.

The factors which predispose to edema formation may be divided into those which act in the tissues and those which affect the kidney. The most important of the tissue factors are the capillary blood pressure, the colloid osmotic pressure, the rate of lymph flow, and the permeability of the capillary walls. As regards the renal factor in edema, it may be stated that retention of water and sodium chloride is the chief quantitative determinant, but the exact mechanism of the latter effect is unknown. The available evidence seems to indicate that such retention is the primary factor in the edema of acute glomerulonephritis and is an extremely important, although possibly secondary, factor in most other types of generalized edema.

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## Section 7—Alterations of Weight

# 21

## Gain and Loss of Weight

Philip Kramer Bondy

Introduction  
General Principles  
Body Weight in Relation to Fluid Metabolism  
    Fluid Retention  
    Diuresis  
Body Weight in Relation to Metabolism of Solids  
    Gain in Weight  
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Summary

### INTRODUCTION

Observations of body weight are of importance in diagnosis and in following the progress of treatment. Although single determinations may reveal deviations from the normal, serial observations, showing trends, are of greater value. The interpretation of weight fluctuations requires an understanding of the factors whose interplay is reflected in changes of body mass—fluid exchange, assimilation of food, energy production, accumulation or breakdown of energy depots, and formation or destruction of functioning protoplasm—i.e., the ebb and flow of all metabolic processes. Since certain influences may tend to increase the weight, while others tend to decrease it, the changes observed clinically represent the resultant of the various metabolic vectors.

What is meant by "normal" weight? The standard to which we usually refer is merely a series of tables representing the average weights of a large number of people. Such tables usually correlate the weight with height, age, and sex. These averages are not applicable to any particular individual; for example, tall, thin people with light bones and small muscles, the so-called "asthenic" or "leptosome" habitus, have relatively low weights as compared to the "normal." On the other hand, the heavily built, muscular, "pyknic" type usually appears overweight by reference to the standard weight charts. Nevertheless, both individuals may be within normal limits for their own body builds. The physician should, therefore, determine the normal weight

for an individual by observing his habitus rather than by reference to an arbitrary standard.

### GENERAL PRINCIPLES

In considering changes of weight, we can conveniently separate the body into two components: liquids and solids. Body water comprises about 70 percent of the body weight.<sup>1</sup> Of the total amount of water in the body, about 20 per cent is extracellular, the rest being confined within the cells. The extracellular fluid includes the plasma, lymph, cerebrospinal fluid, and intercellular tissue juices. Under pathologic conditions there may be appreciable collections of fluid in the subcutaneous tissues, or in the peritoneal, pleural, and pericardial cavities. All extracellular water contains sodium as its major cation, and the movement of water outside the cells is intimately concerned with the movement of sodium. Extracellular fluid is not retained unless sodium is retained, and when the excretion of sodium increases, extracellular water is lost. Since the excretion of sodium is influenced by many factors, changes of extracellular fluid volume commonly cause alterations of body weight.

Intracellular fluid is a component of the intracellular protoplasm. As a part of a complicated colloid system, it is intimately bound with the cellular protein. Changes of intracellular water are, therefore, usually secondary to changes of tissue protein. Under circumstances of dehydration, intracellular fluid may be released to the extracellular compartment; but such shifts affect only a minor portion of the intracellular fluid volume.

Four solid components of the body must be considered: minerals, carbohydrates, proteins, and fats. Most of the weight of the minerals is found in the bones. Carbohydrate does not ordi-

<sup>1</sup> Recent studies by newer methods suggest a considerably lower fraction for the body water. (Editor)

narily make up much of the total body weight, since it can be stored only in small amounts as glycogen. When excessive amounts of carbohydrate are assimilated, they are converted to fat. The body fat consists of the complex lipids, which represent only a small part of the total body fat and are found in all cells of the body, and the neutral fat, which is deposited in depots. (It is recognized that the term "depot" is a relative one. Fat depots are not static, but are constantly undergoing dissolution and replacement. From the standpoint of the total metabolic balance, however, it is sufficiently accurate to consider fat as an inactive storage tissue.) Fat is a convenient chemical for storage of extra energy, since it weighs less than half as much per calorie as does either carbohydrate or protein.

Protein, the major component of the cellular protoplasm, is not stored in any type of inactive depot. A portion of the ingested protein is incorporated in the functioning tissue; the rest is converted to either fat or carbohydrate and metabolized as such. Since protoplasm contains both water and protein in a rather constant proportion, the deposition of protein involves the retention of intracellular water. Approximately 4 Gm. of water are needed for each gram of protein. For this reason, the retention of protein equivalent to 1000 calories causes a weight gain of 1200 Gm., whereas the formation of fat deposits equal to 1000 calories causes a weight gain of only 110 Gm.

The caloric intake necessary to maintain the body weight depends upon the basal metabolic rate and upon the subject's activity. If sufficient food is assimilated to permit the subject to carry on his activities, no change in weight takes place. The food requirement is increased if growth is occurring. In a general sense, growth means the formation of new tissues—of new protoplasm. Growth, therefore, occurs in the fetus, whose requirements must be supplied by his mother, in the growing child, and in the adult engaged in sufficiently arduous work to cause him to form larger muscles and bones. In each of these circumstances, weight is gained. If more cells are not being made, the extra caloric intake is stored as fat.

When inadequate amounts of food are eaten, the subject must supply the deficit from his tissues. If possible, he will burn his fat stores. The body, however, cannot utilize fat as its sole

source of energy. Small amounts of carbohydrate must be catabolized, even under starvation conditions. The stores of carbohydrate are small and are exhausted after a few days of dietary restriction. When the dietary carbohydrate is inadequate, protein is broken down to provide the necessary carbohydrate. Since no storage depots of protein are known to exist, the catabolism of protein to produce the minimal required carbohydrate means breakdown of functioning cells. This protein breakdown proceeds, regardless of the amount of fat available for metabolism, as long as the carbohydrate intake remains inadequate. When the fat stores are totally exhausted, the body must depend on protein for the entire energy requirement, and as a consequence there is rapid destruction of tissue.

From this discussion of general principles of alterations of weight we shall proceed to discuss specific factors controlling the direction of weight changes in various physiologic and pathologic conditions.

#### BODY WEIGHT IN RELATION TO FLUID METABOLISM

**Fluid Retention.** An increase in the extracellular fluid volume may be found in diseases which interfere with the normal excretion of sodium. Of these, the most important are congestive heart failure, acute glomerular nephritis, toxemia of pregnancy, and cirrhosis of the liver. In each of these diseases, sodium is retained and the extracellular water increases. If the quantity of retained fluid is large, the water retention is clinically evident. When less water is retained, the only sign of water retention may be a weight gain, which is due to "inapparent" edema.

Water retention is influenced by factors other than the sodium metabolism. Diseases causing a diminished plasma protein, such as cirrhosis, starvation, and the nephrotic syndrome, are associated with retention of extracellular fluid. Plasma proteins serve to maintain the osmotic pressure of the blood, and act to counteract the intracapillary hydrostatic pressure. When a decrease in the plasma albumin occurs, the osmotic pressure drops, the ability of the blood to pull fluid from the extracellular fluid spaces into the venous end of the capillaries is reduced, and edema formation tends to occur. The edema is mirrored by an increase in the body weight. Similarly, such local diseases as thrombophlebi-

tis, or lymphedema, may cause increases in body weight by local extracellular fluid retention.

An interesting type of weight fluctuation occurs during the course of the menstrual cycle. During the latter part of the month, just before the onset of menstrual flow, most women gain a small amount of weight because they retain water. At the onset of the flow a diuresis occurs and the weight returns to the normal level. These weight changes are apparently the result of fluctuations in the secretion of progesterone, the corpus luteum hormone. Although weight fluctuations during menstruation are not usually noticeable clinically, the tendency to retain water in the premenstrual phase of the cycle may cause clinical edema in patients already tending to be edematous. Thus a patient with acute glomerular nephritis may appear to be having an acute exacerbation of her symptoms just before her menstrual period, merely because of premenstrual water retention.

Two mechanisms may cause water retention in myxedema. There is a characteristic gelatinous water retention associated with increased intercellular fluid protein content; and, in addition, congestive failure, refractory to digitalis but responding dramatically to thyroid hormone, may be seen. Occasionally, patients with myxedema have ascites without clinical evidence of heart failure.

**Diuresis.** In a patient who has retained salt and water, procedures causing a release of water cause a loss of weight. Diuresis may be produced by rest and digitalization in patients with heart disease, or it may occur spontaneously in recovery from acute glomerulonephritis. In patients with the nephrotic syndrome, diuretic crises occasionally occur without obvious cause, and large amounts of weight may be lost rapidly. An increase of water excretion may also occur after the administration of diuretic drugs. It is possible to cause a loss of weight by the restriction of salt intake, a measure particularly useful in the treatment of patients with congestive failure and early toxemia of pregnancy.

When edema has occurred as a result of reduced plasma albumin levels, restoration of the protein levels produces a diuresis and loss of weight. Large quantities of human albumin or plasma are often given intravenously in the treatment of nephrosis and cirrhosis of the liver, in an attempt to produce a diuresis. Frequently,

patients edematous as a result of the hypoproteinemia of undernutrition lose weight when fed an adequate diet. This paradoxical loss of weight is due to the loss of water which has been retained as a result of the low plasma protein level. Later, when the plasma albumin has returned to normal and the edema has been evacuated, the patient's weight again begins to rise as a result of the formation of new protoplasm. The weight curve is a valuable indication of the effectiveness of diuretic therapy, but obviously must be interpreted in accordance with the above considerations.

In addition to loss of weight as a result of the excretion of abnormally accumulated water, weight loss may result from dehydration of a previously normal patient. For example, in cholera and other severe diarrheas, weight may be lost as a result of the water which is passed through the bowel. Excessive sweating may cause loss of weight.

The severe polyuria characteristic of uncontrolled diabetes mellitus may cause dehydration and weight loss, especially if acidosis supervenes and vomiting reduces the fluid intake. Patients with Addison's disease are subject to severe crises of dehydration as a result of vomiting, diarrhea, and the uncontrolled sodium diuresis characteristic of adrenocortical insufficiency. In both of these diseases, however, the loss of weight attendant upon loss of water is acute, and is usually complicated by loss of weight due to destruction of tissues.

### BODY WEIGHT IN RELATION TO METABOLISM OF SOLIDS

In order to maintain its weight, the organism must assimilate sufficient calories to satisfy the requirements of its basal metabolic rate plus its activities. The basal metabolic rate is determined by many factors. Of these, the thyroid hormone is the most important. Hyperactivity of the thyroid increases the rate of activity of body processes, and reduction of thyroid activity reduces them. Fever also increases the metabolic rate, as do certain tumors, especially the lymphomas and leukemias, even in the absence of temperature elevation.

The requirement of energy in excess of that needed to satisfy the basal metabolism is determined by the activity of the organism. Sedentary workers require much less food to maintain their

body weight than do laborers, while growing bodies need extra food to supply the materials for building protoplasm.

**Gain in Weight.** The caloric intake is often quite unrelated to the caloric requirement. What we eat is determined by our appetite; and this, in turn, is more often a reflection of habit and custom than of physiologic requirements. Certain families and cultures place great emphasis on food, and, as a result, many of their members overeat. A man who has been physically active all his life and who suddenly changes to a sedentary occupation may continue to eat as much as when he was active. His habitual appetite causes him to overeat and tends to produce obesity. At the same time, disuse of his muscle mass causes a shrinkage of muscle protein. The result may be that no great change of weight occurs, though the individual becomes flabby.

Certain individuals have increased appetites as a result of psychiatric factors. Such persons use food as a substitute for the satisfaction they should normally obtain from other emotional sources. In this respect, they are similar to alcoholics, who use alcohol as a substitute for such normal sources of satisfaction as their friends, their families, or success in their work.

A third, rare cause of increased appetite is hyperinsulinism. As a result either of a tumor of the islet cells of the pancreas or of diffuse hyperplasia of the islets, with an increased secretion of insulin, there is a tendency for the blood sugar to drop to hypoglycemic levels. The patient soon discovers that he can protect himself by eating excessive amounts of food. Since the hypoglycemia does not interfere with the utilization of glucose, the patient eats more than his requirement and gains weight. The deposition of fat is enhanced by the effect of the excess insulin, which tends to increase fat production from glucose. As a result, such individuals are often extremely obese.

A fourth type of increase of appetite is a result of lesions of certain areas of the hypothalamus. Experimental animals subjected to such lesions develop voracious appetites. The syndrome occurs occasionally in human beings following encephalitis. The obesity which results is due simply to the devouring of huge quantities of food. When the food intake is restricted to normal levels, the patient or animal does not gain weight.

**OBESITY.** Obesity occurs when excessive fat stores are accumulated. This common and dangerous condition aggravates the symptoms of certain degenerative diseases; it may actually be a cause of certain derangements of the cardiovascular and renal systems. Arteriosclerosis can be produced in experimental animals by overfeeding. Obese patients who have heart lesions tend to develop congestive failure earlier; their failure is more severe and is less amenable to therapy than in slim people having similar cardiac lesions. Hypertension in obese people often can be alleviated by reduction of weight.

It is a well-known fact that diabetes mellitus and obesity are closely allied. There is some experimental evidence that obesity can actually cause diabetes. Weight reduction in the obese diabetic frequently will result in improvement, to the extent that the disease may be controlled entirely without insulin. On the other hand, the daily insulin requirement of a diabetic increases when he gains weight.

The function of the reproductive system is often disturbed by extreme obesity. Women who are very fat may suffer from either hypermenorrhea or amenorrhea. Sterility is occasionally seen in males who are very obese, and libido is often reduced. Dietary restriction with weight reduction causes return of these functions to normal.

Although the distribution of adipose tissue may be affected by certain endocrine abnormalities, it is important to stress the fact that obesity is not directly caused by endocrine disease. Fat cannot be deposited except by the assimilation of more food than the body requires. The only way in which endocrine disease may contribute to obesity is by reducing the metabolic rate; this may be observed in myxedema or hypopituitarism. Yet myxedematous patients are sometimes emaciated because their appetites are reduced more than their metabolism; and patients with hypopituitarism, with its resulting hypometabolism, are often cachectic.

It has long been a clinical opinion that the caloric requirement in certain individuals is lower than would be expected on the basis of their activity and basal metabolic rate. Such persons are alleged to become stout even though eating no more than the normal individual. Careful examination of this problem, however, has shown that obesity does not occur unless the caloric intake is greater than the metabolic requirement.

**GROWTH.** In addition to the development of increased depots of fat, weight may also be gained as a result of increases of the functioning tissue, the bones and muscles. This may take place during normal growth and maturation, or as a result of exercise. It is common knowledge that laborers usually have larger muscles than have clerks. The skeletons of people who have done manual labor are heavier than the skeletons of sedentary individuals.

**PATHOLOGIC GROWTH DUE TO ENDOCRINE DISEASE.** Increase in the bulk of the functioning tissue may result from hyperactivity of the acidophilic cells of the anterior hypophysis producing the pituitary growth hormone, causing either acromegaly or gigantism. In these diseases there is an increase in size of all functioning tissue. The bones become thicker and may grow longer if the epiphyses are not fused. The liver, spleen, kidneys, heart, tongue, and other organs also become enlarged. The increased weight is the result of a larger amount of functioning tissue. A similar mechanism accounts for the weight gain and exaggerated muscular development found in children or females having a tumor producing androgenic hormone. Adrenocortical tumors, arrhenoblastomas of the ovary, and rare testicular neoplasms can produce this adrenogenital syndrome.

In summary, therefore, weight may be gained as a result of increased body tissue. When the increase is a result of the assimilation of excess food, fat is laid down and obesity occurs. An increase in the functioning tissue, the muscles and bones, represents a physiologic process except in the abnormal situation of acromegaly, gigantism, or the adrenogenital syndrome.

**Loss of Weight.** Weight loss as a result of decreased body tissue may also be separated into loss of storage tissue and loss of functioning tissue. In this case, however, the separation is somewhat more arbitrary. It has already been pointed out that loss of fat stores cannot be separated entirely from protein and carbohydrate breakdown.

**INADEQUATE FOOD INTAKE.** Loss of adipose tissue may occur as a result of a reduced caloric intake. The restricted diet used for weight reduction should supply adequate vitamins and minerals, proteins, and the necessary minimum of carbohydrate. When these essentials are lacking, the patient begins to starve. Starvation may

occur as a result of inability to obtain food, or because of any of a number of diseases which make it impossible for the body to assimilate what is eaten. Of these, neoplasms of the upper portion of the intestinal tract, including especially the esophagus, are of importance, as are lesions which interfere with the digestion and absorption of food. Chronic pancreatitis, gastritis, and biliary obstruction interfere with the normal secretion of digestive juices, reduce the efficiency of digestion, and permit food to be lost in the feces. If a large segment of the small intestine is removed, either by surgical procedure or by a shunting fistula, the absorbing surface is decreased and inadequate amounts of food are assimilated. The same effect may occur when severe diarrhea causes the intestinal contents to pass through the small bowel so rapidly that absorption is incomplete. Diarrhea may itself be the result of malnutrition, as in pellagra or sprue, in which case the inadequate nutrition is further aggravated by loss of nourishment in the stools. On the other hand, the diarrhea may be primary, as in chronic amebic dysentery, idiopathic ulcerative colitis, bacillary dysentery, tumors of the intestines, or tuberculosis, with the malnutrition as a secondary result.

Starvation may also arise from prolonged anorexia. Loss of appetite may result from many factors, of which probably the most common is infection. During acute infections, such as dysentery, pneumonia, or typhoid fever, the patient loses his appetite. In chronic infections, the loss of appetite, although less severe, may still be dangerous because it exists over a long period of time. It is especially important in such diseases as tuberculosis and rheumatoid arthritis, where weight loss may be of major importance. Certain neoplasms also commonly cause loss of appetite, particularly the advanced stages of cancer when the carcinoma is seeded throughout the body; but anorexia may also occur in cancer of the stomach or where the pain caused by the tumor is so great as to interfere with appetite.

Certain endocrine disorders are characterized by anorexia and weight loss, an example being Addison's disease. When the pituitary gland is destroyed by operation, infarction, or neoplasm, there is commonly a severe loss of weight. This syndrome is known as Simmonds' disease.

Psychic disturbances may cause a profound loss of appetite known as anorexia nervosa. The

resulting starvation is accompanied by muscular wasting, low basal metabolic rate, hypotension, and amenorrhea. This syndrome may be difficult to differentiate from Simmonds' disease.

Undernourished individuals are notably susceptible to infections. This may be a result of poor vitamin intake, but to some extent it probably reflects an insufficient supply of proteins. In the absence of adequate supplies of protein, the body may be unable to build the special antibody globulins, and specific resistance to infectious agents may be impaired.

**ABNORMAL FOOD UTILIZATION.** Loss of weight may also occur even with a normal caloric intake, as the result of increased caloric requirements. Fever is a particularly important cause of increased food requirement. For each degree centigrade rise in body temperature, there is an increase of approximately 13 per cent in the body metabolism. As a result, patients who have prolonged fever burn up their stores of fat and rapidly lose weight. This is particularly serious when the fever is accompanied by anorexia, as in the case of severe rheumatoid arthritis or tuberculosis.

In hyperthyroidism the basal metabolic rate rises, and simultaneously the efficiency of the body in utilizing foodstuffs is impaired. However, as a result of the increased metabolism the patient usually also develops an increased appetite. The combination of weight loss and good appetite should suggest the diagnosis of hyperthyroidism or diabetes.

Wasteful utilization of food may also cause loss of weight. In diabetes mellitus, for example, the ability of the body to utilize glucose is impaired, the blood glucose level rises, and large amounts are lost in the urine. Since, in severe diabetes, there is also a breaking down of tissue proteins to augment the glucose supplies, the patient with uncontrolled diabetes requires a large caloric and high protein intake in order to maintain his weight. In this condition, as in hyperthyroidism, we see the combination of weight loss in the presence of good appetite.

Although, for the most part, we consider weight loss as the result of loss of adipose tissue, it should be recognized that all of the circumstances which we have mentioned as capable of reducing the adipose tissue may also cause a loss of functioning tissue. The most important cause of primary depletion of muscle and bone is disuse.

In patients put to bed for long periods of time—e.g., in the treatment of fractures or of arthritis—the muscles atrophy and the bones become decalcified. This loss of functioning tissue may be disguised by a gain in adipose tissue, so that there is no loss of total weight.

Functioning tissue may also be lost as the result of inadequate local tissue nutrition. For example, patients with congestive heart failure frequently have muscular atrophy. Children with congenital heart disease may be stunted in growth. Patients with chronic pulmonary disease often are underdeveloped as a result of long-standing inadequate blood oxygenation. Severe chronic anemias, such as sickle-cell anemia or chronic hemolytic anemia, may be complicated by reduced growth, and by loss of weight during crises.

## SUMMARY

Although a simple weight measurement is useful in determining whether a patient's weight is normal, the trend of weight over a period of time yields more information. The factors causing changes of weight include alterations of the metabolism of fluids and of solid body components. Extracellular fluid changes are determined by fluctuations in the sodium metabolism, while the variations of intracellular fluid are controlled by the protoplasmic protein concentrations.

Carbohydrate, a rapidly available store of energy, is not stored in large quantities; protein is present in the body as functioning protoplasm. Excess assimilated food is, therefore, changed to fat and stored in the adipose tissue.

The caloric requirement depends on the basal metabolic rate and the physical activity of the body, including growth. When the appetite exceeds the caloric requirement, weight is gained. Appetite depends most on habit, and is greatly influenced by psychic factors. Such metabolic diseases as hyperthyroidism and diabetes mellitus also cause increased appetite. When obesity occurs, degenerative diseases such as diabetes mellitus and arteriosclerosis are aggravated.

Normal growth, increased musculature due to exercise, and pathologic growth seen in certain endocrine disorders all cause weight gain by increase of functioning protoplasm.

Weight is lost when the amount of food assimilated is inadequate for the caloric requirements of the body—i.e., in starvation, severe anorexia, or

digestive disturbances. When the caloric requirements are increased, as in diabetes mellitus and hyperthyroidism, weight may be lost despite a hearty appetite.

The physician, in evaluating body weight, must first decide whether his patient is normally nourished, referring to the patient's habitus rather than to arbitrary standards. By serial determinations, the trend of the body weight is observed. Correlation of these data with clinical observations indicates the relative importance of fluid and of tissue in causing the weight change. Since several factors may be operating simultaneously, with conflicting effect, weight changes

are useful only when combined with careful clinical study; but, when properly understood, the trend of body weight is valuable in diagnosis, in following the course of disease, and in evaluating the effectiveness of therapy.

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## Pallor and Anemia

M. M. Wintrobe

Significance of Pallor  
Pathogenesis of Anemia  
Symptomatology of Anemia  
Detection of Anemia  
Study of a Patient with Anemia  
Classification of Anemia  
Management of Anemia

### SIGNIFICANCE OF PALLOR

The color of the skin depends on many factors, which include the thickness of the epidermis, the quantity and type of pigment contained therein, and the number and degree of patency of the blood vessels, as well as the quantity and nature of the hemoglobin carried within them. Even the nature and fluid content of the subcutaneous tissue are significant factors. It is obvious, therefore, that pallor does not necessarily indicate that anemia is present.

A sallow complexion is present in certain individuals, as it was in their forebears before them, and may exist in the absence of any true anemia; the flush of excitement, on the other hand, or constant exposure to the sun and wind, may produce an appearance which masks an underlying anemia. Physicians, at the turn of the present century, spoke of "rosy" chlorotics, as well as of green and pale ones. The number and pattern of distribution of the finer blood vessels vary in different individuals, and in the same person vasoconstriction may produce the appearance of pallor, whereas other factors, such as exercise, for example, may lead to the appearance of a "healthier" color. Certain disorders may affect the skin in such a way that a pallid appearance is produced, even though anemia is absent. These disorders include scleroderma, the various nephrotic states, and myxedema. The last two, however, may be accompanied by actual anemia.

### PATHOGENESIS OF ANEMIA

Anemia may be the result of loss of blood or the consequence of its excessive destruction. It

may be caused by a deficiency of materials necessary for the formation of red cells, or it may result from a fault in the process of formation of red cells.

Anemia due to blood loss may be acute or chronic. In the former, its nature is usually obvious, although sometimes a large hemorrhage may have occurred under conditions which do not reveal themselves readily. Hemorrhage in the gastrointestinal tract, as from a peptic ulcer, may be dramatic in its symptomatology and may be so severe as to cause shock; it may be insidious in character and may occur without the development of pain or of symptoms pointing clearly to the gastrointestinal tract. Hemorrhage into one of the serous cavities can cause puzzling symptoms and signs: profound anemia may develop suddenly and icterus may even eventually appear, as the result of absorption of blood from a serous cavity.

Chronic loss of blood occurs most commonly from the pelvic organs in females and from the gastrointestinal tract in the male. A common cause of chronic posthemorrhagic anemia in certain parts of the world is infestation with the hookworm.

The "life cycle" of the red corpuscle is thought to be about 120 days. The whole red cell mass is replaced every four months. There is a continuous destruction of red corpuscles which is balanced by formation of red cells in equal degree. Excessive destruction of red corpuscles may occur suddenly or may be a chronic, long-continued process. These "hemolytic anemias" may thus be acute or chronic. They will be discussed in Chapter 249.

For the construction of red corpuscles, amino acids and protein, as well as iron, are important. In addition, the precursors of porphyrin, such as glycine and acetic acid, are required. Certain minerals such as copper and cobalt are concerned

in erythropoiesis, and under experimental conditions in animals it can be shown that anemia will develop when they are lacking. Perhaps still other minerals are involved. Certain of the B vitamins are important in erythropoiesis. These include pyridoxine, "folic acid" (pteroylglutamic acid), and vitamin B<sub>12</sub>, and possibly riboflavin, nicotinic acid, and pantothenic acid are concerned as well. Of these, a hemopoietic effect in man has been demonstrated only in the case of "folic acid" and B<sub>12</sub>. Quite possibly, the other B vitamins are available in sufficient amounts, even under the extraordinary conditions in which man sometimes finds himself. The relationship of the "extrinsic factor" of Castle, the antipernicious anemia liver substance, "folic acid," and its conjugates, and B<sub>12</sub> is not yet clear, but it appears that B<sub>12</sub> is intimately related to the "extrinsic factor" and to the antianemic principle, and it seems likely that the presence of "folic acid" is essential for the hemopoietic activity of liver extract or B<sub>12</sub>.

The role of ascorbic acid in relation to anemia has not yet been established clearly, in spite of the fact that at one time it was thought that a specific anemia results from deficiency of vitamin C. As to the hormones, much is suspected and little is known. It is well recognized that, with myxedema, anemia may be associated, and that after successful treatment of myxedema by the administration of desiccated thyroid the anemia ultimately disappears. Substances may be produced in the spleen which influence erythropoiesis. However, not only is their nature obscure but their existence is uncertain.

In man it is clear that anemia can occur as the result of iron deficiency. Lack of the antianemic principle present in liver and, perhaps, deficiency of other related substances such as pteroylglutamic acid, results in the development of macrocytic anemia. Pyridoxine deficiency anemia has never been demonstrated in man, and the relationship of riboflavin and of nicotinic acid to hemopoiesis in man is not clear. Copper deficiency may, perhaps, occur sometimes in infants, but in the adult its occurrence is doubtful. Cobalt deficiency has not been described in man.

Without doubt, protein deficiency results in anemia in man, but since there exists in the body a "dynamic equilibrium" of the proteins, the deficiency of protein must be very great before hemoglobin production suffers. The role of the

specific amino acids in erythropoiesis in man remains to be worked out.

It should be pointed out that deficiency of substances concerned in erythropoiesis may be the result not only of a deficiency of the factor or factors in the diet but also may arise from their faulty absorption or may be due to metabolic demands which are in excess of supply.

In addition to these means whereby anemia may develop, there exist one or more mechanisms associated with infection and chronic disease which lead to anemia, the nature of which is still quite obscure. It has been proposed that the anemia of chronic infection may be related to a disturbance in iron metabolism. The pathogenesis of the anemia associated with chronic renal disease is an enigma. Other causes of anemia are listed in table 18.

In any given patient with a chronic ailment accompanied by anemia one frequently finds that more than one factor has played a role. Thus, in any long-standing illness, there may be

Table 18  
ETIOLOGIC CLASSIFICATION OF ANEMIA

1. Loss of blood
  - a. Acute posthemorrhagic anemia
  - b. Chronic posthemorrhagic anemia
2. Excessive destruction of blood
  - a. Hemolytic anemias of intra- and extracorporeal origin
3. Deficiency of factors concerned in erythropoiesis
  - a. Iron deficiency
 

Also experimentally, and in certain animals, copper and cobalt deficiencies
  - b. Protein deficiency
  - c. Deficiency of various B vitamins
 

Experimentally, pyridoxine, niacin, pteroylglutamic acid deficiencies; possibly also riboflavin and pantothenic acid deficiencies

Clinically, anti-pernicious anemia principle, "extrinsic factor" (B<sub>12</sub>?) deficiencies: pernicious anemia and related macrocytic anemias
4. Some fault in the construction of red corpuscles
  - a. Anemia associated with infection
  - b. Anemia associated with various chronic diseases (renal, etc.)
  - c. Inhibition of the blood-forming organs or physical injury: plumbism, other poisons, irradiation
  - d. Anemia associated with myxedema
  - e. Anemia associated with splenic disorders: "hypersplenism"
  - f. Anemia possibly resulting from mechanical interference with the bone marrow: myelosclerosis, other "myelophthisic" anemias, leukemia
5. Congenital "dystrophies" of the erythron:
  - a. Congenital hemolytic jaundice
  - b. Sickle-cell anemia
  - c. Mediterranean anemia

a nutritional deficiency due both to faulty intake and to disturbed absorption from the alimentary tract; blood loss may be an added factor; furthermore, some metabolic disturbance, such as the one suggested in relation to the anemia of chronic infection, may exist as well. Sometimes, excessive blood destruction still further complicates the picture.

### SYMPTOMATOLOGY OF ANEMIA

Anemia may be present in severe degree and yet may be associated with few or no symptoms; on the other hand, mild grades of anemia may be found and yet symptoms are prominent. The development of symptoms in association with anemia depends on: (1) The causative disorder; (2) the rapidity with which anemia has developed; and (3) the degree of reduction in the oxygen-carrying power of the blood, as well as the extent of change in total blood volume.

The nature of the condition which has led to the development of anemia is important, since disorders leading to anemia may—of themselves—cause pronounced symptoms which attract attention early; whereas other conditions are of such a nature that they are not likely to be detected until the effect of oxygen want, due to reduced oxygen-carrying power, becomes a factor. If anemia has developed so rapidly that there has been little or no time for physiologic adjustment, symptoms of oxygen want are likely to be prominent and to appear comparatively early; on the other hand, if the anemia has been insidious in onset, the adjustment may be so good that the red cell count may be even as low as 2 million cells per cubic millimeter, or the hemoglobin as low as 6 Gm. per 100 cc., without sufficient functional embarrassment occurring for the patient to appreciate his true condition.

When anemia is caused by the sudden loss of blood, the most prominent symptoms are those resulting from the reduction of the total blood volume, and they are relieved in large measure when the loss of blood is replaced by absorption of fluid from the tissues or by the artificial introduction of fluid or red cells. When there is rapid destruction of blood, the chief symptoms are those connected with the disposal of the products of blood destruction—namely, hemoglobinuria and jaundice. There may also be fever and even abdominal pain. When the anemia is caused by

faulty formation of blood, its onset is much more insidious than in the above circumstances, and the symptoms are referred chiefly to the respiratory, circulatory, neuromuscular, and gastrointestinal systems.

**Respiratory System.** Respiratory symptoms in patients suffering from anemia are often noticeable only following exertion or excitement, although when the anemia is profound there may be dyspnea and rapid breathing even at rest in bed. Respiratory complaints are also dependent on associated myocardial changes and alterations in the cardiovascular system in general.

**Cardiovascular System.** Manifestations referable to the cardiovascular system depend on the severity of the anemia, the age of the patient, the rapidity of onset of the anemia, and the capacity of the cardiovascular system for adjustment. Anemia is one of the commonest causes of palpitation, shortness of breath, and pallor. If very severe, shock may develop. In chronic anemia, moderate dyspnea and palpitation may be the only symptoms related to the cardiovascular system, but, in certain cases, symptoms of congestive failure, angina pectoris, or intermittent claudication may be found as well.

Clinical evidences of an adjusting circulation in cases of anemia include a rapid heart rate, increased arterial pulsation, and increased pulse pressure; even capillary pulsation in the finger tips may be found. The heart may be dilated. An increase in cardiac rate and in the velocity of blood flow results in greater minute volume output and shortened circulation time, and the cardiac output is increased. It is when these physiologic adjustments encroach on the reserves of the body that the clinical picture of cardiac failure ensues. Edema is a frequent accompaniment of anemia, and hemic murmurs are common in anemia of moderate severity. The causes of the edema are multiple. These include the hypoproteinemia which may accompany the anemia and diminished tissue oxygen tension leading to increased capillary permeability. There is also a hemodynamic disturbance associated with dilation of the heart which in turn is the consequence of the increased cardiac output demanded by the anemia and the myocardial anoxemia produced by the deficiency in red corpuscles. The reduction in the number of circulating red corpuscles is, of itself, of little importance in altering the osmotic pressure of the blood. Severe anemia

may produce systolic murmurs at the apex and, very rarely, diastolic blows at the base. Other physical signs associated with anemia may be a lateral displacement of the left cardiac border, downward extension of the liver edge, basal rales in the lungs, and liver tenderness. Over the vessels of the neck a curious humming sound, the *bruit de diable*, may be heard.

**Neuromuscular System.** Headache, vertigo, faintness, increased sensitivity to cold, tinnitus or roaring in the ears, black spots before the eyes, muscular weakness, and easy fatigability and irritability are common symptoms associated with anemia. Restlessness is an important symptom of rapidly developing anemia. Drowsiness develops in severe anemia. Headache due to anemia may be so severe as to simulate meningitis. Delirium is seldom seen except in pernicious anemia, and in the terminal stage of leukemia. Retinal hemorrhage is by no means infrequent.

Paresthesias are common in pernicious anemia and they may be accompanied by signs and symptoms of extensive peripheral nerve and spinal cord degeneration. They may also be encountered in chronic hypochromic anemia but, in the latter, spinal cord degeneration is very rare. In leukemia, involvement of cranial and peripheral somatic nerves occurs, but it is then almost always due to pressure or infiltration.

**Alimentary System.** Loss of appetite is not unusual as an accompaniment of anemia. Nausea, flatulence, abdominal discomfort, constipation, diarrhea, vomiting, or abnormal appetite may also be found. In pernicious anemia and, less often, in chronic hypochromic anemia, glossitis and atrophy of the tongue and papillae are common. In the latter condition, in particular, dysphagia may be found. Necrotic lesions in the mouth and pharynx may develop in patients with aplastic anemia, in granulocytopenia, and in acute leukemia.

**Genitourinary System.** Menstrual disturbances, most often amenorrhea, in the female, and loss of libido in the male, are frequently encountered in severe anemia. In other instances, excessive menstrual bleeding accompanies anemia. Slight proteinuria and even evidence of distinct renal functional impairment may be seen in association with anemia.

**Nutritional State.** If the quantity of superficial fat is the criterion, the nutritional state may appear to be moderately or well preserved, in

spite of the presence of anemia. In severe anemia the basal metabolic rate may be moderately increased. Fever of mild degree is common when anemia is severe. A well-marked febrile reaction is characteristically found when there is rapid blood destruction.

**Spleen.** Enlargement of the spleen is rather frequent in various anemias of long standing. It is seen, in particular, in pernicious anemia, in chronic hypochromic anemia, and in the various hemolytic anemias, as well as in such conditions as leukemia, in which the spleen is specifically involved in the disease process.

So striking are its manifestations and—in certain parts of the country—so common is the disorder, that special mention needs to be made of sickle-cell anemia. This condition exemplifies more than any other how varied the symptoms of anemia can be. The cardiac manifestations of sickle-cell anemia may be so pronounced as to be indistinguishable from those of rheumatic heart disease. Pain in the extremities may add to the confusion with rheumatic fever. Crises of abdominal pain have led to unnecessary operations many times, and the effects of thrombosis in the central nervous system have often raised the question of some neurologic disorder. Yet all of these, and still other bizarre symptoms and signs which are encountered in this disorder, can be attributed to sickle-cell anemia alone.

#### DETECTION OF ANEMIA

The presence or absence of anemia is determined by the examination of the blood, but its existence may nevertheless be suspected and its degree even estimated with fair accuracy by proper examination of the patient. The skin itself, as already indicated, is an unreliable index of anemia; the mucous membranes (if not inflamed), the nail beds, and the palms of the hands are more dependable. The color of the conjunctivas may be very helpful, but one should not be misled by a coexistent conjunctivitis. The gums are not so useful as would be expected, for they may contain pigment or may be inflamed; furthermore, the pressure of the upper lip on the gums may produce some blanching if constriction of vessels results as the lip is retracted. Unless the hand has been held in an awkward position or has been exposed to cold or excessive heat, the nail beds and the palms of the hands will reveal anemia if much exists. In the palms the color of

the creases is especially noteworthy, for they retain their red color even after the intervening skin of the palms has become definitely pale; when their color is lost, the hemoglobin may be judged as being below 7 Gm. per 100 ml.

When anemia has been long standing, the skin may be seen to have lost its normal elasticity and tone, and is dry and shriveled in appearance; the hair may be thin and without luster, and may show early graying. Especially in chronic hypochromic anemia, the nails lose their luster, become brittle and break easily, and may actually become concave instead of convex.

Purpura and ecchymoses may be present in the skin and mucous membranes. When nutritional deficiency is present, in addition, fissures may be found at the corners of the mouth, the mucous membranes may be shiny and red, the tongue is red and atrophic, seborrheic accumulations may be found about the nose ("sharkskin"), and erythematous lesions may be present on the hands, face, neck, and elbows.

The presence or absence of anemia can be determined from the red cell count, the hemoglobin or the volume of packed red cells as measured in the hematocrit. Of these procedures, the measurement of hemoglobin is the simplest but, unfortunately, hemoglobinometers are often imperfectly calibrated. Almost as simple, technically, and much more accurate as an index of anemia (or polycythemia), is the measurement of the volume of packed red cells. When this is measured in the hematocrit, additional information becomes available which is extremely useful in the routine survey of a patient. This includes the sedimentation rate of the red corpuscles, the volume of packed white cells and platelets, and the icterus index. If 5 ml. of blood is collected from a vein in a mixture of ammonium and potassium oxalate (6 mg. of the former and 4 mg. of the latter per 5 ml. of blood), blood is available for a number of quantitative determinations. If the sedimentation rate is increased or if the volume of packed white cells is abnormally great or abnormally thin, the white cell count can be determined without the necessity of obtaining more blood from the patient. If the volume of packed red cells is abnormal, red cell counts and hemoglobin can be determined, and the average volume and hemoglobin content of the red cells calculated. If the volume of packed platelets is abnormal, these can be enumerated, and if the

color of the plasma appears unusual, the icterus index can be measured or a clue is obtained which suggests the need for other chemical determinations. Blood smears must be made directly from the finger. These should be examined in all instances of suspected anemia, for the morphology of the cells can serve as a valuable clue to the nature of the anemia, and may be used to check the calculated mean corpuscular constants.

### STUDY OF A PATIENT WITH ANEMIA

Since anemia is a symptom, it is evident that the patient with anemia requires thorough examination. The *history* must be complete and must, in particular, give attention to the following details:

1. The possible occurrence of blood loss, either acute and in large amounts or chronic and long continued.
2. The diet, particularly with reference to the intake of foods rich in protein, vitamins, and minerals.
3. The presence or absence of symptoms suggesting an underlying disease such as chronic renal disease, chronic infection, or malignancy.
4. In the case of a child or adolescent, the rate of growth.
5. In the case of a woman, the nature of the catamenia (amount of flow, duration, and frequency); the number of pregnancies and abortions; the occurrence of excessive postpartum hemorrhage and the duration of lactation.
6. In certain cases, the possibility of exposure to poisons of various types. In this last regard, attention must be given not only to the patient's occupation and its possible hazards but also to hobbies which may result in exposure to poisons, to possible exposure to insecticides, and to the taking of drugs which may be harmful (arsenic, sulfonamides, gold, etc.).

The *physical examination* must likewise be thorough. The examination of the skin and mucous membranes has been referred to already. The fundi of the eyes should be examined, for they may reveal hemorrhages or the exudates characteristic of chronic renal disease or of leukemia. The tongue may be atrophic and the mucous membranes may reveal purpuric spots. A thorough check needs to be made for evidence of glandular enlargement, and it is good practice to palpate the bones. If done systematically this

may reveal tenderness in the sternum or nodules or tenderness in the ribs. In any condition leading to bone marrow hyperplasia, localized tenderness over the sternum is usually encountered if systemically sought out. In cases of multiple myeloma one may find nodules or tenderness in the ribs. The heart cannot be ignored, for it may give evidence of hemic murmurs or may yield the first clue to the existence of a subacute bacterial endocarditis. The liver and spleen must also be examined carefully and the kidneys must be given attention, for it is not unusual for hypernephroma to cause an obscure anemia. Neither the pelvic nor the rectal examination can be neglected, for these may yield the first indication as to the nature and cause of the anemia. The nervous system, particularly in cases of macrocytic anemia, is likely to reveal abnormalities of significance.

The physical examination may need to be supplemented by roentgenography. A roentgenographic film of the chest may reveal unsuspected mediastinal enlargement, while roentgenograms of the bones may lead to the discovery of tumors or of periosteal elevations suggesting leukemia.

The *laboratory examination* may well commence with the collection of 5 ml. of blood from a vein, as described already, together with a few blood smears. The discovery of anemia, as indicated by a reduced volume of packed red cells, should be followed by red cell counts and a hemoglobin determination, and from these can be calculated the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. These should be checked by examination of the blood smear. In the latter may be found evidences of exaggerated erythropoiesis such as polychromatophilic red corpuscles, macrocytes, and even nucleated red cells. Evidences of disturbed red cell formation, such as poikilocytes, Cabot rings, and Howell-Jolly bodies, may also be found, or the smear may reveal an unsuspected protozoal parasite (e.g., malaria). An increased reticulocyte count gives evidence of physiologically stimulated red cell formation.

The fact should not be overlooked that the hemopoietic system functions as a physiologic unit. Consequently, when red cell formation is stimulated, it is found as a rule that there is, in addition, increased leukopoiesis and an increase in the quantity of platelets. Thus, following acute

blood loss, there may be not only reticulocytosis but also moderate or even marked leukocytosis accompanied by an increase in the younger forms of leukocytes not ordinarily seen in such numbers in the blood ("shift to the left"). The quantity of platelets is also likely to be increased.

When erythropoiesis is impaired, owing to iron or to liver factor deficiency, one finds evidence of disturbed leukocyte and platelet formation as well. Thus, in pernicious anemia, leukopenia is a common accompaniment of the anemia and is usually associated with relative lymphocytosis and the presence of multisegmented polymorphonuclear leukocytes. Thrombocytopenia often exists as well.

Evidence of increased red cell destruction must also be sought out. The clue to this is generally given by the appearance of the plasma which, in cases of increased blood destruction, is distinctly icteric. The Van den Bergh reaction reveals this to be of the "indirect" type, and examination of the urine in such cases reveals an increased quantity of urobilinogen (see p. 204). It is useful, where the facilities exist, to measure the quantity of urobilinogen excreted in the stool as well. In relation to increased blood destruction, it is again important to look upon the hemopoietic system as a physiologic unit. Increased blood destruction, except in certain types of chronic hemolytic anemia, is accompanied not only by the chemical evidence just mentioned but also by reticulocytosis, leukocytosis, and thrombocytosis (see p. 1191).

The anemia associated with chronic infection or with chronic renal disease, like aplastic anemia due to the action of a poison, is differentiated from the anemias due to nutritional deficiency and the anemias due to exaggerated blood destruction by the lack of evidence of hemopoietic activity. Thus the anemia is usually normocytic and is accompanied by relatively little poikilocytosis or anisocytosis; reticulocytes are normal in number and nucleated red cells are not found in the blood smear; the leukocytes are not altered in number from the normal except in so far as they may represent a reaction to the underlying disorder.

Knowledge of the chemical processes concerned in erythropoiesis has not yet reached the point where chemical examination is of great practical value in the recognition and differentiation of the various types of anemia. Ultimately,

this may become as important as the morphologic study of the blood. Thus the *plasma iron* content is reduced below the normal in cases of iron deficiency, in association with the anemia of chronic infection, and in various types of anemia in which blood regeneration is active. The plasma iron content is increased in pernicious anemia in relapse and in hemolytic anemias. However, the increased plasma iron of pernicious anemia in relapse falls to values below normal during the time when blood regeneration is occurring as the result of liver therapy. In certain circumstances, particularly in the anemia of chronic infection, the content of *free protoporphyrin in the erythrocytes* is increased. In this type of anemia the *serum copper* content is also in excess of the normal.

Table 19

CONDITIONS IN WHICH VARIOUS TYPES OF REACTION  
MAY BE OBSERVED, AS DEMONSTRATED BY BONE  
MARROW ASPIRATION

<i>M:E Ratio Increased</i>	<i>Nonmyeloid Cells Increased</i>
Myeloid forms of leukemia	Other forms of leukemia
The majority of infections	Multiple myeloma
	Metastases from carcinoma, etc.
	Gaucher's disease, Niemann-Pick disease
	Aplastic anemia (usually relative increase only)
<i>Normoblastic Hyperplasia</i>	<i>Megaloblastic Hyperplasia</i>
Hemorrhagic anemias	Pernicious anemia
Iron deficiency anemia	Sprue, idiopathic steatorrhea, resection of small intestine (certain cases)
Hemolytic anemias	Tropical macrocytic anemia
Mediterranean anemia	Nontropical nutritional macrocytic anemia
Cirrhosis of the liver	Macrocytic anemia with <i>Diphyllobothrium</i> infestation
	Megaloblastic anemia of infancy
	Megaloblastic anemia of pregnancy
	"Refractory megaloblastic" anemia
	"Achrestic" anemia

When the patient has been studied thoroughly in the manner indicated above, the number of instances in which *examination of the bone marrow* will be required is small. In table 19 various types of reaction which may be observed by differential counts on aspirated bone marrow are listed. In the study of bone marrow as obtained by sternal, iliac crest, spinous process, or rib

puncture, consideration should be given to the following:

1. What is the myeloid:erythroid (M:E) ratio? By this is meant the proportion of leukocytes of the myeloid series to nucleated red cells of all types.

2. If the M:E ratio is decreased—that is, if the proportion of nucleated red cells is greater than normal—what is the character of the erythroblastic predominance? Is it normoblastic or megaloblastic?

3. Is there an increased number of cells other than those of the myeloid or erythroid series? These include lymphocytes, plasma cells, reticulum cells, and other forms (myeloma cells, carcinoma cells, Gaucher cells, etc.).

4. Since megakaryocytes form so small a proportion of the cells of the bone marrow, specific attention should be given them and a number of preparations of marrow should be examined. Do they appear to be increased or greatly decreased in number? Is their morphology normal?

5. If little material has been obtained by puncture, is the bone marrow aplastic, fibrotic, or otherwise abnormal, the material obtained being essentially only blood? In such a case, trephine biopsy may be necessary.

In table 20 are given normal values for the differential nucleated cell count of bone marrow obtained by puncture, and representative findings in a number of conditions are presented. These must be regarded only as examples of findings in typical cases and do not give the range of variation in disease. The latter obviously depends on the stage of the disease and the presence or absence of modifying factors, and is difficult to present in tabular form.

Although in all cases the material obtained by sternal puncture is of interest, bone marrow examination is an essential aid in diagnosis only in a limited number of conditions. These include aleukemic leukemia, multiple myeloma, Gaucher's and Niemann-Pick diseases, and unusual cases of macrocytic anemia. In the last-mentioned condition the demonstration of megaloblasts is very useful since it suggests a liver factor type of deficiency. In "aleukemic" leukemia, the bone marrow findings are similar to those encountered in cases in which the blood picture is also characteristic and thus the correct diagnosis may be discovered when, until the marrow examination was made, doubt existed. In

Table 20  
REPRESENTATIVE DIFFERENTIAL COUNTS OF BONE MARROW OBTAINED BY PUNCTURE

<i>Types of Cells</i>	<i>Normal*</i> <i>Average and Range</i>	<i>Leukemia, Acute†‡</i>	<i>Leukemia,‡ Chronic Myelocytic</i>	<i>Leukemia,‡ Chronic Lymphocytic</i>	<i>Multiple Myeloma§</i>	<i>Pernicious Anemia</i>	<i>Hemolytic Anemias</i>	<i>Iron Deficiency Anemia</i>	<i>Purpura Hemorrhagica</i>
Myeloblasts.....	2.0 (0.3-5.0)	50.0-95.0	4.0	..	0.5	0.8	0.8	0.5	..
Promyelocytes.....	5.0 (1.0-8.0)	..	10.0	0.8	1.8	2.7	3.0	2.0	1.5
Myelocytes									
Neutrophilic.....	12.0 (5.0-19.0)	..	26.0	1.5	1.8	7.7	8.0	9.0	8.0
Eosinophilic.....	1.5 (0.5-3.0)	..	2.0	0.7	..	0.8	2.0	0.8	..
Basophilic.....	0.3 (0.0-0.5)	..	0.4	0.2	..	0.3	..	..	..
Metamyelocytes.....	22.0 (13.0-32.0)	..	22.0	8.0	3.3	14.5	18.0	15.0	15.3
Polymorphonuclear neutrophils.....	20.0 (7.0-30.0)	..	29.0	8.5	62.0	14.5	9.0	28.0	31.0
Polymorphonuclear eosinophils.....	2.0 (0.5-4.0)	..	0.8	1.0	3.5	0.5	0.6	0.2	0.5
Polymorphonuclear basophils.....	0.2 (0.0-0.7)	..	0.4	3.0	1.2	0.2	..	..	0.2
Lymphocytes.....	10.0 (3.0-17.0)	..	1.4	60.0	13.0	9.5	10.0	1.0	2.5
Plasma cells.....	0.4 (0.0-2.0)	..	..	..	4.5§	0.2	0.4	0.7	0.8
Monocytes.....	2.0 (0.5-5.0)	..	0.2	..	0.2	0.3	..	..	..
Reticulum cells.....	0.2 (0.2-2.0)	..	1.2	1.5	1.0	2.0	2.6	0.8	..
Mitotic figures.....	0	..	0.2	0.3	..	2.7	1.0	..	..
Abnormal cells.....	0	..	..	..	..	..	..	..	..
Megakaryocytes.....	0.4 (0.03-3.0)	..	..	..	..	..	..	..	0.2¶
Megaloblasts.....	0	..	..	..	..	40.0	..	..	..
Pronormoblasts.....	4.0 (1.0-8.0)	..	..	0.2	..	..	5.0	..	4.0
Normoblasts.....	18.0 (7.0-32.0)	..	2.4	14.3	9.0	3.0	43.0	40.0	36.0
M:E ratio.....	4:1 (3-5:1)	..	40:1	1.5:1	8:1	1:1.5	1:1	1.4:1	1.5:1

\* Adapted from M. M. Wintrobe: "Clinical Hematology," 2d ed., Philadelphia, Lea & Febiger, 1946.

† The immature forms are listed in the table as myeloblasts merely as a matter of convenience. In acute lymphoblastic leukemia the cells are lymphoblasts, not myeloblasts. Often it is difficult to distinguish the various immature leukocytic cells seen in acute leukemia. The essential point is the great preponderance of very young forms.

‡ The bone marrow picture in "aleukemic leukemia" is similar to that of leukemia of the various types, whether or not changes can be demonstrated in the blood.

§ The characteristic cells in multiple myeloma differ somewhat from typical plasma cells in that the nuclear chromatin is relatively fine and the wheel-spoke arrangement of the chromatin is not present; the cytoplasm is basophilic and bright blue, not blue-green as in the plasma cell. A perinuclear clear zone is unusual.

¶ Although the number of megakaryocytes may not appear to be increased, in typical purpura hemorrhagica the majority (64 per cent in the case cited) have no platelets about them and most of the remainder (32 per cent) have very few.

|| The most significant changes are shown in *italics*.

addition to these disorders, it may be added that, in cases of parasitic diseases such as kala-azar, the causative organisms may be discovered in the bone marrow when they cannot be found in any other way. Again, the cells of metastatic lesions may be demonstrated by sternal puncture.

In aplastic anemia it is the negative character of the marrow material which may be helpful. In cases suspected of being instances of "atypical leukemia," "agnogenic myeloid metaplasia," or "hypersplenism," sternal puncture followed by trephine biopsy may support one of these diagnoses or, instead, may reveal myelosclerosis or myelofibrosis.

It is customary to think of the blood in relation to a unit of volume. It is not unusual to forget that the sample examined is only a portion of the whole mass of blood. Fortunately, the unit obtained by venipuncture or from the finger is reasonably representative, and it is rarely necessary to measure the total blood volume; nor is it often practicable to perform the latter determination. It is necessary, nevertheless, to bear in mind the concept of total blood volume and to recall that an increase in the fluid portion of the blood—that is, an increase in the total plasma volume—may give a false impression of anemia, the total red cell mass having been reduced little or not at

Table 21  
MORPHOLOGIC CLASSIFICATION OF ANEMIAS

<i>Class and Severity</i>	<i>Number of Red Corpuscles</i>	<i>Mean Corpucular Volume, Vol. R.B.C.</i>	<i>Mean Corpucular Hemo- globin, Hb. R.B.C.</i>	<i>Mean Corpucular Hemo- globin Concentration, Hb. Vol.</i>	
<b>MACROCYTIC:</b>					
Slight.....	—	+	+	0	Red cells increased in volume; mean corpucular hemoglobin proportionately increased; increase in size and hemoglobin content of red cells roughly inversely proportional to number of cells; mean corpucular hemoglobin concentration remains normal throughout or may be slightly reduced
Moderate.....	--	++	++	0-	
Severe.....	---	+++	+++	0-	
<b>NORMOCYTIC:</b>					
Slight.....	—	0	0	0	Reduction in the number of red cells without any, or at most only slight, increase in mean corpucular volume and mean corpucular hemoglobin; mean corpucular hemoglobin concentration normal throughout
Moderate.....	--	+0	+0	0	
Severe.....	---	+0	+0	0	
<b>SIMPLE MICROCYTIC:</b>					
Slight.....	—	0	0	0	Reduction in volume and hemoglobin content characteristic less marked than reduction in number of red cells; mean corpucular hemoglobin concentration normal or only slightly reduced
Moderate.....	--	—	—	0-	
Severe.....	---	—	—	0-	
<b>HYPCHROMIC MICROCYTIC:</b>					
Slight.....	0	—	—	—	Reduction in volume and hemoglobin content characteristic more marked than reduction in number of red cells; mean corpucular hemoglobin concentration characteristically reduced.
Moderate.....	—	—	—	—	
Severe.....	—	—	—	—	

Hb. indicates the quantity of hemoglobin in grams per 1000 ml. of blood; Vol. = volume of packed red cells in milliliters per 1000 ml. of blood; R.B.C., the number of red cells in millions per cubic millimeter. + increase; - decrease; 0 no change from the normal; 0- no, or only slight, decrease; +0 slight or no increase. The amount of increase or decrease is indicated by the number of plus or minus signs, respectively.

all. Of even greater importance is the fact that extracellular fluid deficit (dehydration) may mask an underlying anemia.

#### CLASSIFICATION OF ANEMIA

Anemia, since it is a symptom, may be classified in various ways. It can be differentiated on the basis of etiology or pathogenesis as outlined in table 18, and it can be classified on morphologic grounds. From one point of view the etiologic

classification of anemia would be the more satisfactory. However, the incompleteness of our knowledge restricts the usefulness of the etiologic classification of anemia; furthermore, certain anemias can be classified on this basis under more than one heading. Since anemia must be classified after the patient's history has been taken and the physical examination as well as the blood examination have been made, there are certain advantages to be gained from a classifica-

tion of anemia centering about morphology. On this basis anemias may be divided into three or four groups: (1) The macrocytic anemias; (2) the normocytic anemias, and (3) the microcytic anemias. These last anemias include a well-defined group, the hypochromic microcytic anemias, and another, referred to as "simple microcytic," because in this anemia the reduction in the hemoglobin content of the cells corresponds to the reduction in red cell size, with the result that the mean corpuscular hemoglobin concentration is not significantly reduced. This morphologic classification is outlined in table 21.

Macrocytic anemias are characterized by an increase in the average volume (M.C.V.) and weight of hemoglobin (M.C.H.) in the red corpuscles. The concentration of hemoglobin in the red cells (M.C.H.C.) remains normal. The macrocytic anemias, in general, are of two types. The most common group is that which results from a deficiency of the antianemic principle present in liver. This type of anemia may be the consequence of a lack of necessary food factors in the diet ("extrinsic factors"), the result of faulty absorption (impaired gastric secretion, chronic diarrhea, etc.), or due to other causes (as indicated in table 22 and as will be outlined fully later [p. 1183]). These conditions, with the exception of the anemia of hypothyroidism and many instances of macrocytic anemia associated with liver disease, respond to treatment with liver extract or related substances. The second group depends on the fact that immature red cells, in general, are larger than their fellow, mature corpuscles. Consequently, in conditions which ordinarily produce normocytic anemia, when there is an accompanying very intense activity of the bone marrow with liberation into the circulation of many immature cells, a temporarily macrocytic anemia develops. This second variety of macrocytic anemia must be distinguished from the first, since, in this type, liver therapy is of no value.

The normocytic anemias are those characterized by red cells of normal average size and hemoglobin content. Theoretically and actually, these are due to: (1) the sudden loss of blood; (2) the destruction of blood, acute or chronic; (3) lack of blood formation; or (4) hydremia, in which event there may be no true anemia.

The simple microcytic anemias, as already mentioned, are characterized by a reduction in

the size of the cells without a significant reduction in their hemoglobin content. This is the least well-defined of the morphologic groups of anemia and is found in association with subacute and chronic noninflammatory disease and in various chronic inflammatory conditions.

Table 22

MORPHOLOGIC AND CLINICAL CLASSIFICATION OF ANEMIA

- I. Macrocytic Anemias (M.C.V.\* 94–160 c. $\mu$ , M.C.H. $\ddagger$  32–50 $\gamma\gamma$ , M.C.H.C. $\ddagger$  32–36%):
  - A. Those related to deficiency of antianemic principle in liver:
    - 1. Pernicious anemia
    - 2. Sprue and other conditions in which intestinal absorption is impaired
    - 3. Nutritional macrocytic anemias ("tropical," etc.)
    - 4. Miscellaneous and less well understood macrocytic anemias (pregnancy, *Diphyllobothrium* infestation, and, possibly, liver disease, hypothyroidism)
  - B. Where there is intense activity of the bone marrow:
    - Conditions usually associated with normocytic anemia (see below)
- II. Normocytic Anemias (M.C.V. 82–92 c. $\mu$ , M.C.H. 28–32 $\gamma\gamma$ , M.C.H.C. 32–36%):
  - A. Sudden loss of blood
  - B. Destruction of blood—acute and chronic hemolytic anemias
  - C. Lack of blood formation—hypoplastic and aplastic or refractory anemias due to poisons, infection, metastases, etc.
  - D. Hydremia—not a true anemia
- III. Simple Microcytic Anemias (M.C.V. 72–82 c. $\mu$ , M.C.H. 23–24 $\gamma\gamma$ , M.C.H.C. 30–36%):
  - Anemia associated with chronic infection, chronic renal disease, etc.
- IV. Hypochromic Microcytic Anemias (M.C.V. 50–82 c. $\mu$ , M.C.H. 12–29 $\gamma\gamma$ , M.C.H.C. 24–32%):
  - Iron deficiency due to:
    - A. Chronic blood loss
    - B. Inadequate intake of iron together with
    - C. Faulty absorption (achlorhydria, sprue, etc.)
    - D. Excessive demands for iron (growth, menstruation, pregnancies)
- V. Mediterranean Anemia

\* M.C.V. refers to mean corpuscular volume.

$\ddagger$  M.C.H. refers to mean corpuscular hemoglobin.

$\ddagger$  M.C.H.C. refers to mean corpuscular hemoglobin concentration.

The hypochromic microcytic anemias are characterized by a reduction below normal in the average volume of the red cells, together with a marked reduction in the concentration of hemoglobin. With the exception of a congenital and hereditary disorder known as Mediterranean anemia, the hypochromic microcytic anemias are the consequence of iron deficiency. This deficiency

may be the result of a lack of iron in the diet, defective absorption, chronic loss of blood, or excessive demands for iron (growth, repeated pregnancies), but it is most often produced by chronic blood loss (gastrointestinal tract, uterus), aggravated by several of the other factors operating in various degrees and combinations. These anemias respond to the administration of iron.

### MANAGEMENT OF ANEMIA

Details of the management of anemia will be discussed elsewhere, in connection with the various types of anemia. It may be emphasized here, however, that adequate management is impossible without the thorough study and classification of the anemia as outlined above. *Liver therapy* is extremely valuable in the macrocytic anemias resulting from a lack of the anti-anemic liver principle. It is valueless in all other types of anemia, even when they are macrocytic (see table 94, p. 1184). The administration of *iron* is eminently effective in relieving the iron deficiency anemias. It is useless in all other types of antianemia. The anemias which are neither due to deficiency of iron nor caused by lack of the anemic principle are most difficult to manage. Iron or liver therapy, vitamins, or combinations of these, given orally or parenterally, are useless and wasteful of the patient's funds and the physician's time. These anemias cannot, in the present state of our knowledge, be relieved without the elimination of the underlying cause. Thus, the anemia of chronic renal disease is difficult to treat because the renal disease itself is usually so unremittent in character. Likewise, the anemia of chronic infection persists as long as the underlying infection continues. Aplastic anemias in which the bone marrow has been damaged, in general carry a very poor prognosis. In some instances the destruction of hemopoietic tissue may not be complete, and in such cases the maintenance of life by transfusion may ultimately be followed by some, or even occasionally by complete, regeneration of bone marrow. The anemia of leukemia is relieved if the leukemic process can be checked by the use of irradiation or chemotherapy. The same is true of the anemia of Hodgkin's disease and other disorders of the lymphoid tissue. In all of these conditions the administration of iron or liver is valueless, and the giving of transfusions is but a temporary measure of limited value.

Except in the management of the circulatory collapse which may be associated with acute blood loss or acute blood destruction, or when blood is given to supply the antihemophilic substance or prothrombin, *blood transfusion* must be regarded as a nonspecific method of treatment. Yet it may be of great value. As specific methods of treatment are discovered, the need for blood transfusion is reduced. Thus this measure is scarcely ever needed in pernicious anemia nor in iron deficiency anemia, even if the anemia is severe, for the patient has had time to become adjusted to the hemoglobin deficiency and can wait for physiologic regeneration. Transfusion is useful in tiding the patient over until other measures may be decided upon or become effective, or until spontaneous recovery occurs. This is true in certain cases of hemolytic anemia, in leukemia, and in purpura hemorrhagica. In matching blood for transfusion in hemopoietic disorders, special care must be taken, for the repeated administration of transfusions may lead to the production of antibodies in such titers that serious reactions may occur. Again, the danger of producing pulmonary edema by overloading the vascular bed must not be overlooked. In cases of aplastic anemia, where the number of transfusions used may become very great, actual hemosiderosis may be produced, since the iron from the introduced red corpuscles is not excreted. It is a good principle, therefore, to err somewhat on the side of giving fewer rather than too many transfusions, since this is but a palliative form of therapy.

*Splenectomy* produces permanent relief of the anemia of congenital hemolytic jaundice and may be valuable in some cases of hemolytic anemia of the acquired type. This is especially true in the more chronic cases and when leukopenia and thrombocytopenia are also present. This operation is the most effective measure for the treatment of purpura hemorrhagica, and it can be helpful in the management of the Banti syndrome. As in the case of other therapeutic measures which are known to be useful in the management of certain hemopoietic disorders, however, splenectomy should not be undertaken without a thorough diagnostic study and full knowledge of the risks involved—the operative mortality, the possibility of postoperative atelectasis or other complications, such as thromboses in association with the marked thrombocytosis which

may develop after operation, and the likelihood of failure to achieve the result desired by this operation.

*General measures* include a well-rounded diet containing the food factors especially useful in blood regeneration, such as animal protein, the B vitamins and iron, as well as all necessary factors, such as ascorbic acid; a reasonable balance between rest and muscular activity; reassurance and understanding care; and the man-

agement of the various complaints by palliative measures as required.

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# 23

## Bleeding

M. M. Wintrobe

Hemorrhage as the Result of Injury of Large Vessels by Trauma or by Erosion from Pathologic Processes  
 Bleeding Due to Generalized Vascular Disorders  
 Fragility of the Skin and Its Blood Vessels  
 Bleeding Due to Defects in Factors Concerned in Blood Coagulation  
 Symptoms Produced by Hemorrhage  
 Mechanisms for Control of Bleeding  
 Study of a Patient with Hemorrhage

Except for that which occurs during menstruation, the loss of blood is abnormal and this symptom, therefore, is a definite indication for a search for disease. As indicated in table 23, bleeding may arise from a great variety of causes, and these may involve any of the systems of the body. This table represents a systematic and logical classification rather than one based on frequency.

The most frequent cause of hemorrhage is that resulting from injury of large vessels by trauma or by erosion from pathologic processes. Less common is that which is attributable to some form of generalized vascular disorder. Very rare are instances of hemorrhage which occur as a result of fragility of the skin and its blood vessels. Defects in the factors concerned in blood coagulation represented a comparatively infrequent cause of bleeding until the therapeutic use of dicumarol and heparin was introduced. The more common causes of hemorrhage are listed in table 24.

### HEMORRHAGE AS THE RESULT OF INJURY OF LARGE VESSELS BY TRAUMA OR BY EROSION FROM PATHOLOGIC PROCESSES

Trauma is one of the chief causes of this type of bleeding. This may lead to external bleeding, and under such circumstances the cause and source are usually apparent. When the bleeding is within the body, the true nature of the condition may not be discovered so readily. A variety of systems of the body may be affected. Intracranial hemorrhage is not uncommon following injury. The symptoms depend on the location of the hemorrhage. Injury to the chest may lead to the fracture of ribs and this, in turn, by damaging the pleura, may lead to hemothorax. Abdominal injury may lead to rupture of viscera, with which some blood loss is associated. The rupture of the spleen in particular, is accompanied by great loss of blood, since this is so vascular an organ. In fracture of the pelvis, severe retroperitoneal hemorrhage may occur.

Hemorrhage in the absence of trauma or of some disorder in the process of coagulation suggests the existence of some pathologic process or of a congenital abnormality. Occasionally, trauma is the precipitating factor inducing hem-

Table 23

## CLASSIFICATION OF CAUSES OF HEMORRHAGE

- I. Injury of large vessels by trauma or by erosion from pathologic processes
- II. Vascular dysfunction:
  - A. Multiple hereditary telangiectasia
  - B. Nonthrombocytopenic purpuras:
    1. Allergic purpuras
    2. Symptomatic purpuras (infections, chronic diseases, chemical and physical agents, scurvy)
    3. Hereditary hemorrhagic diathesis (thrombasthenia)
    4. Miscellaneous forms of purpura (purpura simplex, purpura fulminans, purpura senilis, purpura cachectica, mechanical purpura, orthostatic purpura)
  - C. Deficiency of vitamins C (scurvy) and (?) P
- III. Fragility of the skin and its blood vessels (Cushing's syndrome) and hyperlaxity of the skin (Ehlers-Danlos syndrome) and other skin disorders (epidermolysis bullosa, etc.)
- IV. Defects in the factors concerned in blood coagulation:
  - A. Quantitative deficiency of platelets (thrombocytopenia):
    1. Essential or primary purpura hemorrhagica
    2. Symptomatic thrombocytopenic purpura
  - B. Qualitative deficiency of platelets or deficiency of a platelet thromboplastin (hemophilia?)
  - C. Diminished prothrombin:
    1. Lack of vitamin K (obstructive jaundice, biliary fistula, impaired absorption from bowel, deficient diet, impairment of bacterial growth in bowel ["Sulfasuxidine," etc.], hemorrhagic disease of the newborn)
    2. Liver damage
    3. Toxin (sweet clover disease of cattle, dicumarol)
    4. Administration of salicylates
    5. Idiopathic hypoprothrombinemias
  - D. Decreased fibrinogen:
    1. Congenital or constitutional fibrinogenopenia
    2. Severe liver damage; rarely in nutritional deficiencies, disorders of the bone marrow, etc.
  - E. Excessive amounts of anticoagulants in the blood:
    1. Heparin; anaphylactoid and peptone shock, effect of irradiation
    2. Dicumarol
    3. Hirudin
    4. Antithromboplastin (anticephalin) (hemophilia?)
    5. Idiopathic (?)

orrhage from vessels which are congenitally abnormal or are already damaged by disease. To list all the possible causes of hemorrhage resulting from pathologic processes is unnecessary, but a number of the most important ones may be mentioned.

In the *nervous system*, hemorrhage may be associated with hypertension or arteriosclerosis. In

younger persons hemorrhage in the nervous system should arouse suspicion of a congenital abnormality, such as an aneurysm in the circle of Willis. Inflammatory disease of the nervous system is rarely a cause of significant hemorrhage. Tumors, likewise, are not commonly associated with hemorrhage, although bleeding into a tumor is by no means unusual.

Hemorrhage from the *nose* is a common symptom. This may be the result of external trauma, but not rarely it is the consequence of local irritation and damage to the mucous membrane. In the presence of an inflammatory process involv-

Table 24

## COMMON CAUSES OF HEMORRHAGE

- I. Trauma to any part of the body
- II. Congenital abnormalities or pathologic processes:
  - A. Nervous system—hypertension, arteriosclerosis, aneurysm in circle of Willis
  - B. Nose, ears, and throat—local irritation, hypertension, skull fracture
  - C. Lungs—tuberculosis, lung abscess, bronchiectasis, tumor
  - D. Gastrointestinal tract—peptic ulcer, esophageal varices, carcinoma of the stomach, ulcerative colitis, hemorrhoids
  - E. Urinary tract—glomerulonephritis, stone, tumor
  - F. Genital apparatus—uterine fibroids, ruptured ectopic gestation

ing the nasal mucous membrane (e.g., diphtheria, streptococcal infections), hemorrhage is likely to occur, especially if trauma is associated. Kesselbach's (Little's) area may become engorged and a varix may develop which is readily made to bleed by mechanical factors. Epistaxis is not unusual in hypertension. This symptom frequently is the initial and even the sole complaint in cases of multiple hereditary telangiectasia. When defects in the factors concerned in blood coagulation exist, as will be outlined below, hemorrhage is particularly apt to occur from the nose.

Bloody mucus, rather than free bleeding, is associated with perforation of the cartilaginous portion of the nasal septum, such as may be produced by syphilis or by chromium poisoning, or may be encountered in typhoid fever. Tuberculous perforation of the bony portion of the septum is not associated with bleeding. Only one type of nasal polyp leads to epistaxis. This is a fibroepithelioma which possesses a wide base and is situated on the septum.

Diseases of the nasal passages and sinuses other

than those mentioned above are rarely a cause of hemorrhage. Trauma is by far the most common cause of bleeding from the *throat*. Hemorrhage from the *ear*, if not due to a direct blow, suggests fracture of the skull.

Hemorrhage from the *lungs* may arise in association with inflammatory processes such as tuberculosis, lung abscess, bronchiectasis, atypical pneumonia, and coccidioidomycosis, or may be associated with the presence of tumors—benign or malignant. When there is consolidation of the lung, as in pneumonia, the sputum may contain blood, but rarely is the blood large in amount. Congestive heart failure, especially when due to mitral stenosis or complicated with pulmonary infarction, is frequently associated with hemoptysis. Hypertension is another, though infrequent, cause. Rare causes of bleeding from the respiratory passages include broncholithiasis and erosion of the respiratory passages by conditions affecting the mediastinum, such as aneurysm of the aorta and disease of the lymph nodes.

It is not always easy to determine whether the patient has coughed up or vomited any blood which has been expelled. Blood coming from the lungs is usually bright red in color and is often frothy, since it has been mixed with air. However, blood coming from the respiratory tract does not always present this classic appearance. Thus, if it comes from an area which is inflamed or congested, aeration may not be good and the blood may be somewhat dark, suggesting material obtained from the stomach. Furthermore, blood from the respiratory passages may be swallowed first and then vomited, with the result that it has all the characteristics of blood coming from the stomach. Blood arising in the stomach is generally dark because of the formation of acid hematin by mixture of hemoglobin with hydrochloric acid. It may be mixed with stomach contents.

By far the most common cause of massive *gastrointestinal bleeding* is peptic ulcer. Ruptured esophageal varices and carcinoma of the stomach, especially the former, are also frequent causes. A hemorrhagic diathesis is the cause of gastric hemorrhage less than once in 100 cases. Hematemesis and melena are discussed in a separate chapter (Chapter 17).

Gastric polyps may give rise to massive bleeding. Although malignant neoplasms of the stomach of the usual type rather infrequently cause

severe hemorrhage, rhabdoleiomyomas have a definite tendency to cause free bleeding, but these are exceedingly rare. A cause of hematemesis hitherto little recognized is hiatus or diaphragmatic hernia. A phytobezoar in the stomach may cause ulceration of this organ and so lead to hemorrhage.

Esophageal varices may be seen in association with the Banti syndrome and in various forms of cirrhosis of the liver. Congenital anomalies in the portal system or thrombosis of the portal vein may have the same effects as cirrhosis by producing portal hypertension and leading to the development of esophageal varices.

Meckel's diverticulum may cause massive hemorrhage from the intestinal tract. Benign polyps of the intestine may lead to blood loss, but this is rarely dramatic or large in amount. Ulcerative malignant processes will likewise cause hemorrhage, but this again is usually of a chronic character. The blood loss associated with inflammatory processes, except in the case of nonspecific ulcerative colitis and typhoid fever, is rarely of significant amount. When intussusception, volvulus, or mesenteric thrombosis is present, a bloody discharge rather than true hemorrhage is found. The rarer forms of tumor of the intestine, such as lymphosarcoma, sometimes cause bleeding. Hemorrhoids, of course, are an important source of blood loss. Large hemorrhages are rare in tuberculosis of the colon but do occur, and then are likely to prove fatal. Of the parasites which may be found in the intestine, the hookworm, *Ancylostoma duodenale*, is an important cause of chronic blood loss. Hemorrhage from the alimentary tract may also be encountered in uremia.

Bleeding from the *urinary tract* (hematuria) may be the result of a variety of causes. Among the more common etiologic factors are glomerulonephritis, and stones or tumors in the bladder or kidney pelvis, such as benign or malignant papilloma of the bladder and hypernephroma of the kidney. A polycystic kidney sometimes produces this symptom. Of inflammatory processes, tuberculosis is the most common cause of hemorrhage from the urinary tract. Hematuria is sometimes seen in association with malignant hypertension. Severe bleeding, even with the production of clots in the bladder, may occur when only prostatic hypertrophy is present, due perhaps to the rupture of a varicose vein on the middle lobe.

When cystitis is severe, much bleeding may also occur. The urinary tract is the commonest site of bleeding complicating dicumarol therapy.

The female genital tract is, of course, an important source of hemorrhage. The various causes will not be considered here, but mention should be made of a common cause of internal bleeding—ruptured ectopic gestation. Much rarer is hemorrhage due to the rupture of an ovarian cyst.

### BLEEDING DUE TO GENERALIZED VASCULAR DISORDERS

This includes some well-defined, as well as certainly vaguely differentiated, conditions associated with bleeding. The condition hereditary hemorrhagic telangiectasia is a vascular anomaly characterized clinically by hemorrhage, and anatomically by multiple dilatations of capillaries and venules which are found in the skin and mucous membranes. The trait is transmitted as a simple dominant by both sexes and is commonly marked by epistaxis, but bleeding may come from telangiectases in any location, such as the tongue or mucous membranes of the mouth or the gastrointestinal, respiratory, or genitourinary tracts. The telangiectases may be pin-point in size or larger; they may form nodular vascular tumors the size of a split pea; and sometimes they are spider-like, particularly in elderly patients. Although these telangiectases are usually quite evident when attention is called to them, not infrequently they are overlooked.

The so-called nonthrombocytopenic purpuras compose a much less well-defined group of conditions associated with bleeding. These can be classified under four headings: (1) allergic purpuras; (2) symptomatic purpuras; (3) hereditary hemorrhagic diathesis (thrombasthenia); (4) miscellaneous forms of purpura.

These conditions will be discussed more fully later (Chapter 226), but it should be stated here that the term "allergic" refers to a group of nonthrombocytopenic purpuras which are characterized by one or more of the common manifestations of allergy, such as erythema, urticaria, or effusions of serum into subcutaneous or submucous tissues or viscera.

~~X~~ Symptomatic "purpura" may be associated with various infections, with chronic disease, with the action of various chemical and animal agents, with scurvy, and with certain skin diseases. Such

infections as subacute bacterial endocarditis, meningococcal sepsis, influenza, scarlet fever, smallpox, measles, and diphtheria, as well as septicemias due to various other organisms, may be associated with various hemorrhagic manifestations. These result, presumably, from capillary damage produced by toxins. Substances have been obtained by autolysis of pneumococci which are capable of producing purpura experimentally. In subacute bacterial endocarditis the purpura is often embolic in origin. A white center may be observed in the hemorrhagic skin lesions. Purpura associated with meningococcal sepsis is due to capillary injury.

Advanced renal or hepatic disease and some instances of acute glomerulonephritis are sometimes associated with purpura. Purpura of the skin and mucous membranes and large subcutaneous extravasations or hemorrhages into the internal organs may be found when there has been acute destruction of the liver. This is due probably to lack of prothrombin and, sometimes, to lack of fibrinogen as well. Hemorrhagic manifestations have been noted in a number of cases of hemochromatosis and are common in Cushing's syndrome.

The use of iodides, copaiba, belladonna, atropine, quinine, bismuth, mercury, phenacetin, salicylic acid, chloral hydrate, and merbaphen has been followed in some cases by the development of purpura without thrombocytopenia. This is probably the result of idiosyncrasy associated with capillary damage. The hemorrhagic effects produced by certain snake venoms are probably due to injury to the endothelial lining of capillaries and small veins.

Hemorrhage in the skin, subcutaneous tissues, and elsewhere is a classic symptom of scurvy.<sup>Drug</sup> The bleeding is attributed to increased capillary permeability rather than to alterations in the blood itself. The bleeding ceases following the administration of lemon juice and similar anti-scorbutic substances. Whether it is caused by lack of ascorbic acid alone or of a second factor, "vitamin P," is not yet clearly established.

A rare hemorrhagic disorder associated with no clearly defined abnormalities in the blood is sometimes called "hereditary hemorrhagic diathesis" or "hereditary hemorrhagic thrombasthenia." This condition will be discussed later (Chapter 226, p. 1207).

Of the miscellaneous forms of purpura not as-

sociated with abnormalities in the blood, there may be included the following:

1. *Purpura simplex*, a term generally applied to instances of mild purpuric skin manifestations unassociated with well-defined abnormalities in the blood.

2. *Purpura fulminans*, a term applied to a very rare form of nonthrombocytopenic purpura which affects children chiefly, and is characterized by sudden onset, fever, symmetric ecchymoses in the skin without hemorrhage from the mucous membranes, and a fatal course of one to four days.

3. *Purpura senilis* and *purpura cachectica*, terms applied to the extravasation of blood in old or ill-nourished individuals in whom no better defined cause of purpura can be found than "capillary weakness."

4. *Mechanical purpura*, which refers to purpuric manifestations associated with violent muscular contractions such as occur in whooping cough or convulsions, with the result that capillaries are ruptured.

5. *Orthostatic purpura*, a term describing purpura which develops in some persons in the lower extremities after prolonged standing. This is presumably due to capillary weakness.

#### FRAGILITY OF THE SKIN AND ITS BLOOD VESSELS

Theoretically, and occasionally actually, hemorrhage may be the result of abnormal fragility of the skin and its blood vessels and hyperlaxity of the skin. This is seen in a very rare disorder known as the Ehlers-Danlos syndrome. Occasionally, hemorrhage, especially from the mucous membranes, is seen in other skin disorders such as epidermolysis bullosa. Still other skin conditions associated with hemorrhagic manifestations are annular telangiectatic purpura (Majocchi's disease), Schamberg's disease, pigmented purpuric lichenoid dermatitis, and angioma serpiginosum. The hemorrhagic manifestations seen in Cushing's syndrome are attributed to fragility of the skin.

#### BLEEDING DUE TO DEFECTS IN FACTORS CONCERNED IN BLOOD COAGULATION

**Theory of Coagulation.** The classic theory of coagulation regards clotting as involving two stages and four essential components, as follows:

1. Prothrombin + Ca + Thromboplastin  
→ Thrombin
2. Fibrinogen + Thrombin  
→ Fibrin

It is becoming clear, however, that this is an oversimplification. Thromboplastin, which is found in all tissue fluids, is a complex factor. It appears to be derived from the interaction of a precursor substance, "thromboplastinogen," and an activating factor or cofactor which is released by the rupture of platelets. The latter occurs readily on contact with a foreign surface. Likewise "prothrombin" is not a simple substance but rather a complex made up of at least two, probably three components. These include a "labile factor" (at first called component A), which becomes inactive after a few days' storage of blood, and a stable factor (component B). The latter is reduced by the administration of dicumarol. The first may be identical with "factor 5" (so called because it represents one more coagulation substance than is postulated in the classic theory based on four factors) and appears to be essential for the conversion of prothrombin to thrombin by thromboplastin and calcium. A third prothrombin component, found lacking in the blood of a family with a hemorrhagic diathesis, may be the one which is reduced in vitamin K deficiency. This has been called the new component A.

With these concepts in mind, bleeding due to defects in the factors concerned in blood coagulation may be classified as follows:

1. **Quantitative Deficiency of Platelets (Thrombocytopenia).** The purpuras associated with a reduction in the number of platelets will be discussed elsewhere (Chapter 226). It will suffice here to state that these conditions can be classed under two headings; namely, (a) "essential" or "primary" purpura hemorrhagica, and (b) symptomatic thrombocytopenic purpura. The latter may be due to the action of various chemical, vegetable, animal, and physical agents, or may be associated with various blood disorders. Occasionally thrombocytopenic purpura develops in certain infections.

Chemical agents causing thrombocytopenic purpura include the organic arsenicals, allyl-isopropyl-acetyl-carbamide ("Sedormid"), gold salts, and benzol, as well as a number of other agents which will be discussed elsewhere. Vegeta-

ble agents include various foods and orris root. Animal agents include certain snake venoms. Among the physical agents may be mentioned roentgen irradiation, radium, and heat stroke.

The blood disorders associated with thrombocytopenic purpura include the various types of leukemia and various anemias such as aplastic anemia, anemia associated with encroachment on the bone marrow by metastases, etc. (myelophthisic anemia), pernicious anemia, and chronic hypochromic anemia. In certain splenic disorders such as the Banti syndrome, Gaucher's disease, Felty's syndrome, hemolytic icterus, and, rarely, in Hodgkin's disease, thrombocytopenic purpura may be encountered. The infections which may occasionally produce this symptom include various septicemias, subacute bacterial endocarditis, typhoid fever, typhus, miliary tuberculosis, smallpox, vaccinia, scarlet fever, and measles.

**2. Qualitative Deficiency of Platelets or Deficiency of a Platelet Thromboplastin.** Bleeding as the result of a qualitative deficiency in the platelets has not yet been conclusively demonstrated, although this mechanism has long been suspected to be the cause of hemophilia. This subject will be discussed later in the section on hemophilia (Chapter 227, p. 1209).

**3. Diminution of the Prothrombin Content of the Blood.** If the prothrombin content of the blood is reduced sufficiently, hemorrhage may occur, since the blood will not clot. Prothrombin deficiency may arise in various ways.

**A. LACK OF VITAMIN K.** It has been clearly established that this vitamin is necessary for the formation of prothrombin. Since the vitamin is fat-soluble, the bile salts are required for its absorption. Consequently, vitamin K deficiency is found when there is complete obstruction of the flow of bile into the intestinal tract, or when a biliary fistula exists. In conditions in which there is impaired absorption from the bowel, as in sprue, vitamin K deficiency may develop. Lack of vitamin K in the diet is an extremely rare cause of vitamin K deficiency, for this vitamin is produced in abundance by bacteria growing in the intestines. When the growth of such organisms is inhibited, however, as in cases in which drugs are given for this purpose, vitamin K deficiency can ensue.

The fetus and the newborn infant receive their store of prothrombin from the mother. After food

has been taken by the infant and bacteria begin to grow in the intestinal tract, these serve to produce vitamin K. In occasional instances an infant may be born with a poor supply of prothrombin, and may suffer severe hemorrhage before it has had an opportunity to produce vitamin K for itself. This is thought to be the reason for the development of the condition called "hemorrhagic disease of the newborn."

**B. LIVER DAMAGE.** Prothrombin is formed in the liver. If liver damage has been severe and long continued, inadequate formation of prothrombin occurs with the result that the process of coagulation is impaired.

**C. TOXINS.** A hemorrhagic disease of considerable economic significance occurs in cattle fed spoiled sweet clover hay. The bleeding apparently is due to the development of hypoprothrombinemia, and ceases promptly as soon as the toxic hay is replaced with a normal diet. The toxic principle in the hay, a coumarin compound, has been isolated and synthesized. It is now used therapeutically, under the name of dicumarol, when it is desired to prevent the coagulation of blood. It is component B of the prothrombin complex which is reduced by dicumarol.

**D. ADMINISTRATION OF SALICYLATES.** When salicylates are given in very large quantities, the prothrombin content of the blood plasma is reduced. The mechanism of this action is not clear, but it is thought to be similar to that of dicumarol. Even when large doses are used therapeutically, however, salicylates are rarely a cause of bleeding.

**E. IDIOPATHIC HYPOPROTHROMBINEMIA.** Several patients have been observed in whom a hemorrhagic diathesis characterized by hypoprothrombinemia was present which could not be attributed to the hitherto recognized causes of hypoprothrombinemia. These cases, therefore, have been classified as "idiopathic." In one such family there was a deficiency of prothrombin component B; in another case "factor 5" or the "labile factor" was lacking; in still another family a third component of the prothrombin complex was missing.

**4. DECREASED FIBRINOGEN.** Lack of fibrinogen, or a significant reduction in the amount of fibrinogen in the blood, is an extremely rare cause of bleeding. Severe liver damage produces impairment in the production of prothrombin before it interferes significantly with the formation

of fibrinogen. Certain drugs such as suramin and perhaps certain dyes and fibrinolysins, may cause a reduction in fibrinogen, and there also has been described a very rare condition known as "congenital" or "constitutional fibrinogenopenia." Less marked reductions in fibrinogen have been observed in occasional cases of pernicious anemia, in chronic myelocytic leukemia, and in other disorders of the bone marrow, as well as in pellagra and scurvy.

**5. Excessive Amounts of Anticoagulant in the Blood.** There is little known concerning the mechanism whereby blood remains fluid within the body. The fact that disease or trauma may alter the vascular endothelium and thus liberate thromboplastin without leading to more than local thrombosis, has led to the supposition that anticoagulant factors are present in blood which probably maintain a dynamic equilibrium with coagulant factors. The nature of such anticoagulant substances is poorly understood. The best-known one, heparin, may not be a physiologic anticoagulant. If it is present in normal blood, it is in small amounts. In anaphylactoid and peptone shock, however, hemorrhage may be due to the presence of excessive amounts of heparin. The incoagulability of the blood following irradiation, as in victims of the atomic bomb explosion, appears to be due to an excess of heparin. Heparin and also dicumarol are used therapeutically as anticoagulants in the management of thrombosis and, in clinical practice, this is the most common form in which excess anticoagulant produces hemorrhage.

Very little is known about other anticoagulants. It has been postulated that excess of a normal anticoagulant, anticephalin, acting as anti-thromboplastin, is responsible for the hemorrhage occurring in hemophilia (p. 1208). Leech extract contains a substance (hirudin) which produces incoagulability of the blood, perhaps through an antithrombin effect. Several cases of abnormal bleeding have been described in which hemorrhage appeared to be due to the presence of an unidentified anticoagulant.

#### SYMPTOMS PRODUCED BY HEMORRHAGE

The symptoms associated with blood loss differ according to whether the loss is large and rapid or relatively slow and long continued. Acute and severe blood loss occurring within a matter of a

few minutes results in syncope, but when the loss occurs over a period of hours the picture of shock is induced. The classic examples are seen in hemorrhage from peptic ulcer or ruptured ectopic pregnancy. The clinical picture is described and the pathogenesis of these manifestations is discussed on page 158 *et seq.*

The acute loss of blood stimulates the hematopoietic system, with the result that the reticulocytes are increased in number and, if the hemorrhage is very severe, even occasional nucleated red cells of the normoblastic type may be found in the circulating blood. At the same time the leukopoietic tissues are stimulated and a marked leukocytosis occurs. This leukocytosis is due to the liberation of cells formed in the bone marrow, with the result that the juvenile neutrophils are increased and even some myelocytes may appear. There is at the same time an increase in the number of blood platelets. Their number may be increased twofold, or even more. When the hemorrhage is entirely within the body, the absorption of the blood may produce hyperbilirubinemia. This, in turn, may result in an increase in the quantity of urobilinogen in the urine and may even be accompanied by noticeable jaundice.

Slow *chronic blood loss* ultimately produces anemia and this, in turn, is associated with the symptoms characteristic of anemia which have been described elsewhere (Chapters 22, 224). The anemia eventually becomes hypochromic and microcytic in type, and, instead of leukocytosis and thrombocytosis, one finds leukopenia with relative lymphocytosis, often accompanied by the presence of multisegmented polymorphonuclear neutrophils. At the same time there may be a somewhat reduced number of platelets. In spite of this "hypoplastic" blood picture, however, if the anemia is severe, occasional small nucleated red cells ("microblasts") will be found.

#### MECHANISMS FOR CONTROL OF BLEEDING

There are several natural mechanisms for the control of bleeding. If tissue is crushed, the tissue juice promotes clotting of blood. The thin walls of the veins collapse, the thicker walls of the arteries retract and become more narrow, and capillary constriction occurs. If the arteries are sufficiently small and coagulation is normal, the blood clot may eventually suffice to stop the flow

of blood. Where there is injury to a large arterial trunk, there may be such a fall in blood pressure that the peripheral circulation diminishes sufficiently to allow the blood to clot. In structures with few elastic and muscle fibers, such as mucous membranes, persistent oozing may take place, especially if there is a coagulation defect, for the contraction of damaged vessels is only temporary and when they dilate once more a firm clot of blood must be present to prevent bleeding.

### STUDY OF A PATIENT WITH HEMORRHAGE

Hemorrhage, if severe, first requires treatment by replacement of the blood which has been lost. Rational treatment beyond this, however, depends on a clear understanding of the cause of the hemorrhage. This entails recognition of whether or not the bleeding is the result of a fault in the process of coagulation, the consequences of dysfunction of the blood vessels, or the effect of trauma or pathologic processes unrelated to disorders of the blood. As is always the case, there is no short cut to the taking of an accurate history and the performance of a complete and thorough physical examination. The differential diagnosis of the causes of hemorrhage other than those concerned with disorders of the blood is beyond the scope of this section, for it entails consideration of disorders which include all the systems of the body. These are dealt with in other sections.

The history may reveal a story of trauma or the symptoms of some disorder of which the hemorrhage may be a symptom. It should also yield information concerning possible exposure to agents which may cause bleeding. In this connection it is necessary to inquire not only about the patient's occupation but also about his or her hobbies, for sometimes these lead to unexpected exposures. Specific inquiry must be made, for frequently the patient does not think of mentioning some insecticide to which he or she may be exposed, or some drug which he or she has been taking from time to time for a number of years. A family history of bleeding should arouse suspicion of such conditions as hemophilia, purpura hemorrhagica, hereditary hemorrhagic telangiectasia, and even of the much rarer conditions—hereditary hemorrhagic diathesis, idiopathic hypoprothrombinemia, and constitutional fibrinogenopenia. The physical examination may

reveal vascular anomalies, as in the case of hereditary telangiectasia, and may indicate the site of hemorrhage.

The examination of the blood should include the determination by reliable methods of coagulation time, clot retraction, prothrombin time, bleeding time, and the platelet count. A tourniquet test should be done as well. Some of these procedures are relatively crude but if carefully performed they are useful, nevertheless. Circumstances in which changes in these tests take place are summarized in table 25.

The *coagulation time* is a measure of the capacity of the blood to clot after it has been removed from the body and has come into contact with something which can initiate the process, such as a surface of glass. Since only a few platelets are needed to initiate clotting, thrombocytopenia is rarely a cause of prolonged coagulation time. The coagulation time should be measured, preferably, in test tubes of uniform size, and a control determination on the blood of a normal person should be made at the same time. In the determination of *prothrombin time*, it is important that a potent thromboplastin be used and that a determination be made on normal subjects at the same time. The test for *bleeding time* is quite simple, but unless it is done carefully a false normal result may be obtained. The bleeding time is a measure of capillary retraction as well as of the capacity of the blood to clot, since the test is based on the effect of a skin puncture in producing bleeding. Thus bleeding time is rarely lengthened in hemophilia even though the coagulation time is prolonged, since capillary retraction is good, and sufficient tissue fluid usually reaches the blood to aid in clotting the blood.

*Platelet counts* are notoriously difficult to perform with accuracy; consequently, the count should be checked by examination of the blood smear, which should reveal gross discrepancies if they exist. Since *clot retraction* depends chiefly on an adequate supply of platelets, delayed retraction suggests thrombocytopenia. The *tourniquet test* is useful in demonstrating decreased capacity of the capillaries to withstand the effects of increased pressure. It probably depends on several factors: the integrity of the capillary endothelial cells, the availability of intercellular cement substances, and the quantity of platelets.

It is important that all four determinations—bleeding time, platelet count, clot retraction

*Table 25*  
CAUSES OF ALTERATIONS IN THE VARIOUS MEASURES OF COAGULATION

Laboratory Finding	Condition	Pathogenesis
I. Coagulation time prolonged	A. Hemophilia B. Hyperheparinemia C. Idiopathic D. Afibrinogenemia E. Action of various anticoagulants (snake venoms, etc.)	Hereditary deficiency of a plasma factor (thromboplastin?) or excess antithromboplastin 1. Anaphylactoid and peptone shock 2. Therapeutic use of heparin 3. Following irradiation (atom bomb) Excess anticoagulants of unknown type 1. Hereditary fibrinogen deficiency 2. Very severe liver disease 1. Hirudin (leech extract) is antithrombic 2. Other substances anticoagulant in other ways
II. Prothrombin time prolonged (coagulation time prolonged if prothrombin less than 10% of normal)	A. Vitamin K deficiency  B. Excess dicumarol C. Idiopathic or hereditary	1. Malabsorption: obstructive jaundice, } "New com- sprue 2. Congenital: neonatal deficiency } ponent A" deficiency 3. Malutilization: liver disease "Component B" deficiency 1. "New component A" deficiency 2. "Component B" deficiency 3. Labile factor or factor 5 deficiency Platelets too few to close capillary defect
III. Bleeding time prolonged	A. Thrombocytopenias of various types B. Any of the factors under I or II if deficiency is very severe C. Hereditary hemorrhagic diathesis	Extreme poverty of blood and tissues in coagulation factor
IV. Tourniquet test positive	A. Infections, allergy, etc. B. Thrombocytopenic purpuras C. Scurvy	Damage to capillary endothelial cells Platelets too few to support capillaries under pressure
V. Thrombocytopenia	Purpuras, primary and secondary	Deficiency of intercellular cement substance See Chapter 226
VI. Clot retraction poor	Thrombocytopenia of various types	Insufficient platelets to induce fibrin contraction

time, and tourniquet test—be carried out. In a classic case of thrombocytopenic purpura the bleeding time is prolonged, the platelet count is reduced, clot retraction is delayed, and the tourniquet test is positive. When these are the findings, one has confidence in the results of each of the tests. When there is a discrepancy between them, one should repeat these determinations and seek out possible sources of error.

In any case of bleeding it is desirable to study the morphology of the red cells and the leukocytes, and to determine the reticulocyte count. An increase of reticulocytes is the response of a normal bone marrow to hemorrhage, and its degree gives a rough index of the severity of the hemorrhage. The lack of reticulocytosis would mean either an inability on the part of the bone marrow to respond, as would be the case in

aplastic anemia, or a less severe hemorrhage than other indications had suggested. The degree of leukocytosis, likewise, is an index of the severity of the hemorrhage and the capacity of the bone marrow to react. A low leukocyte count, in the face of a severe hemorrhage, would suggest some abnormality of the marrow, as might be the case in "aleukemic" leukemia or in aplastic anemia. The presence of very immature leukocytes suggests "aleukemic" leukemia, but it must be borne in mind that a few myelocytes form part of the picture of a vigorous response to hemorrhage.

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# 24

## Enlargement of Lymph Nodes and Spleen

M. M. Wintrobe

### Causes of Lymph Node Enlargement

### Differential Diagnosis of Lymph Node Enlargement

### Enlargement of the Spleen

### Differential Diagnosis of Splenomegaly

There are some 500 to 600 lymph nodes in the body, and these vary from less than 1 mm. to 1 to 2 cm. in size. These structures afford mechanical filtration for the lymph stream, removing cellular debris, foreign particles, and bacteria which may have gained access to the lymph from the various structures drained by the lymph channels. In the normal individual very few lymph nodes are palpable, even on careful physical examination. However, the access of disease-producing bacteria and certain viruses sets up an inflammatory reaction in the nodes, and various types of malignant cells can proliferate there. It has been aptly stated that in the exercise of their function the lymph nodes may sacrifice their own integrity for the welfare of the organism as a whole.

These structures are also the site of formation of lymphocytes and of antibodies. Furthermore, the cells of the reticuloendothelial system contained within the nodes can revert to the task of blood formation. This is known as myeloid metaplasia, and is a reflection of embryonal hematopoietic potencies. This reaction is also accompanied by lymph node enlargement.

### CAUSES OF LYMPH NODE ENLARGEMENT

Enlargement of the lymph nodes may be purely local or it may be widespread. Such enlargement may be accompanied by all the signs of acute inflammation, such as heat, reddening of overlying skin, and tenderness; and the glands, instead of remaining discrete, may fuse with one another as the result of the perilymphangitis which occurs. Necrosis may even ensue, and may be followed by rupture of the nodes and the formation of a sinus. On the other hand, very great enlargement of the lymph nodes may take place in the absence of any signs of inflammation whatever, and the glands may remain discrete at the same time. Enlarged lymph nodes may be extremely hard,

or only moderately so, or may even be soft or cystic. When mediastinal, abdominal, or other deeply placed lymph nodes are affected, their enlargement may be first discovered as the result of the pressure such enlargement may produce. Thus acute mediastinal lymphadenitis in young children may lead to a stridor, cyanosis, and dysphagia; and noninflammatory enlargement of the nodes in this region often leads to one or more of these signs. Again, if the condition is inflammatory in character, fever and leukocytosis and other signs of systemic involvement may be the first evidences of disease. When it is not due to infection, the glandular enlargement may be huge and evidences of systemic involvement may be wholly lacking; or, instead, wasting, anemia, and even fever, may be more prominent than the glandular swelling.

The chief causes of lymph node enlargement are listed in table 26. The strategic location of

Table 26  
CHIEF CAUSES OF LYMPH ENLARGEMENT

1. Infections:
  - a. Acute, regional: Etiologic agents include streptococcus, staphylococcus, Durey's bacillus, *Bacillus tularensis*, *Treponema pallidum*, virus of lymphopathia venereum, *Pasteurella pestis* (plague)
  - b. Acute, systemic: Infectious mononucleosis, measles, rubella, chickenpox, etc.
  - c. Chronic: Tuberculosis, syphilis
2. Allergic reactions: Serum sickness
3. Congenital abnormalities (lymphangiomas)
4. Primary lymph node diseases: Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, etc.
5. Leukemia
6. Metastases from malignant disease in breast, stomach, etc.

lymph nodes along the lymph channels makes them likely to be involved in a variety of infections, both acute and chronic. The enlargement of the anterior cervical nodes in association with streptococcal sore throat, and enlargement of the epitrochlear node draining a digit which is infected, are well-known examples of a regional

reaction to local infection. The satellite node of tularemia is another example, and the buboes of lymphogranuloma venereum and of plague may also be noted. Again, many types of acute generalized infection are accompanied by lymphadenopathy which may be local or widespread. Lymph node enlargement frequently accompanies measles, rubella, mumps, and chickenpox. This is usually most prominent in the anterior cervical chain. In infectious mononucleosis, generalized lymph node enlargement is characteristic, but cervical glandular enlargement is often more striking than that found elsewhere in the body. Lymphadenopathy may be encountered in acute anterior poliomyelitis, especially in infants and children, in whom, in particular, the development of an acute infection of almost any variety is frequently accompanied by some degree of lymph node enlargement. Other acute infections are accompanied by adenopathy, but this may not be easily discernible (for example, the mesenteric lymph node enlargement which is seen in typhoid fever).

Of the chronic infections, tuberculosis and syphilis are the most common causes of lymphadenopathy. In tuberculosis the cervical, mediastinal, or mesenteric glands are most often involved. The enlargement usually is slowly progressive and is easily confused with that caused by Hodgkin's disease. However, tuberculous glands are frequently tender, firm, and adhere to one another. Sometimes breakdown of the overlying skin occurs, leading to the production of a stubborn, draining sinus. Rarely the lymph node enlargement is acute and rapidly developing, and in such cases the glands may remain discrete and freely movable. In relation to syphilis, the firm, painless swelling in the regional lymph nodes draining the primary lesions, the generalized, firm, shotty, nontender nodes which accompany the secondary stage, and the glandular swelling of various degrees which may accompany the late stages or the congenital form, may be mentioned. Other chronic infections in which glandular swelling may be prominent include fungous infections and filariasis. Sarcoidosis, a disorder which in many ways resembles tuberculosis and Hodgkin's disease and which by many is regarded as a form of tuberculosis, often must also be considered. In Boeck's sarcoid the pre- and postauricular lymph nodes, the submaxillary, submental, epitrochlear and para-

tracheal glands are more often affected than in Hodgkin's disease. A history of involvement of the eyes and of the parotid glands (uveoparotid fever) suggests sarcoid, and punched out areas in the small bones of the hands and feet may be demonstrable by roentgenography (see Chapter 232).

Serum sickness should not be overlooked as a cause of lymphadenopathy, particularly since this is usually accompanied by fever. Again, it may be noted that trauma, in the form of running and jumping, has been known to lead to painful swelling of the inguinal and femoral lymph nodes. Of congenital abnormalities which may lead to lymphoid enlargement, simple or capillary lymphangiomas, cavernous lymphangiomas, and the cystic form (cystic hygroma) may be mentioned.

Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma are frequently classed under the single heading of primary lymph node diseases or lymphomas because, clinically, they are usually indistinguishable. In these conditions the lymph node enlargement is characteristically localized at first, and only as the disease progresses does wide dissemination occur. The glandular enlargement is usually discrete and firm, and ranges greatly in degree. When the adenopathy becomes widespread, nodes may be discovered in locations where the presence of lymphoid tissue may not have been suspected. Such cases of lymph node enlargement are distinguished from those due to leukemia chiefly by the changes in the blood characteristically seen in the latter condition, but also by the asymmetry of the swellings which is often seen in the "lymphomas." In leukemia lymph node enlargement is usually generalized and symmetric, although, especially in acute leukemia, adenopathy may be much more prominent in the neck than elsewhere.

Metastatic enlargement of lymph nodes, as a rule, is distinctly localized and the glandular swelling ordinarily is very hard. Such enlargement may involve nodes which are easily discovered, such as those of the axilla in cases of carcinoma of the breast. It may be more often heard about than seen, such as Virchow's sentinel node above the clavicle in cases of carcinoma of the stomach or other abdominal organs. Or the adenopathy may exist in some region of the body inaccessible to physical examination but discoverable only by roentgenography or through

the indirect effects of pressure produced by enlargement of the nodes.

Lymph node hyperplasia is encountered in Addison's disease, hyperthyroidism, and hypopituitarism, in which conditions the adenopathy is noteworthy since it contrasts with the tendency for lymph node atrophy found in association with inanition due to other causes.

### DIFFERENTIAL DIAGNOSIS OF LYMPH NODE ENLARGEMENT

It should be evident, from this discussion, that the discovery of the cause of glandular enlargement requires a thorough examination of the patient. It is important, of course, to determine the extent of the adenopathy. The systematic examination should especially include careful palpation of the cervical regions, the epitrochlear regions, the arms (for swelling of brachial nodes), the axillas, the lateral borders of the chest, the inguinal and femoral regions, and the popliteal spaces. The location of the glandular enlargement may suggest the site of origin of the disease and sometimes may give some clue as to its nature. Acute cervical adenitis should direct attention to the mouth and pharynx, mastoid adenitis to scalp infections, axillary adenitis to the upper extremity and the breast, epitrochlear enlargement to involvement of the ulnar side of the hand or forearm, and inguinal swelling to the lower extremities and genitalia. Supraclavicular gland enlargement, it may be noted, may result from infection in the thumb and index finger as well as in the neck. If the gland is hard and not tender it may be the seat of tumor. Lymph drainage to this node is such that, if the right node is enlarged, some primary process in the chest should be suspected; whereas enlargement of the left supraclavicular node should direct attention to the abdomen. Enlargement of the inferior deep cervical glands in the posterior triangle of the neck is more often due to Hodgkin's disease, or secondary to malignancy, than due to an infection arising in the throat. The occipital glands are not infrequently affected in rubella and in secondary syphilis. The finding of discrete, nontender nodes in regions where lymph nodes are rarely palpated, as along the brachial artery or in the femoral (as distinguished from the inguinal) region, should arouse suspicion of the existence of a systemic disorder involving the lymphatic system, such as leukemia.

The general examination of the patient must also be painstaking, for sometimes secondary glandular enlargement may be much more prominent than the primary cause. Thus, for example, cervical metastases from a nasopharyngeal tumor usually overshadow the primary growth, which is characteristically small and easily overlooked unless a careful nasopharyngoscopic examination is made. The study of the patient should include careful palpation of the sternum for tenderness, and of the abdomen for splenic enlargement, as well as examination of the chest for evidence of mediastinal tumor. Rectal and pelvic examination must not be overlooked.

Important laboratory procedures include the serologic test for syphilis, examination of the blood for agglutination reactions, blood culture and culture of the throat, sputum, and other possible sources which might reveal infection, as well as examination of the blood and sometimes of the bone marrow for morphologic evidences of disease. Skin tests, such as tuberculin, histoplasmin, and coccidioidin, may also need to be performed, culture of the lymph nodes may be helpful occasionally, and roentgenograms may have to be taken of the lungs, the gastrointestinal system, the kidneys, or other structures. In chronic forms of lymph node enlargement, biopsy of a node may be necessary, especially when it is a matter of differentiating the various types of primary lymph node disease.

### ENLARGEMENT OF THE SPLEEN

It is very rare that one can palpate the spleen in a person who is entirely normal, although it must be admitted that very occasionally a person is encountered in whom the spleen is palpable, and yet even prolonged observation fails to reveal any evidence of disease. How often this may occur is difficult to state.

The pulp of the spleen is composed of (1) anastomosing strands of lymphoid tissue, (2) a reticular network and branching multipolar cells which are placed about blood sinuses and intermingle with the strands of lymphoid tissue, and (3) lymphocytes, granulocytes, and erythrocytes. The spleen is a very vascular organ and is capable of changing substantially in size, depending on its content of blood. It functions as a reservoir for blood and is concerned in blood destruction. During embryonic life it plays an important part in blood formation, and the

potentialities of this organ for blood formation persist even in adult life. Lymphocytes are normally produced in the mature animal by the Malpighian corpuscles of the spleen, and monocytes may also arise in that organ. In addition, the spleen may play a role in the defense mechanism of the body, perhaps largely through antibody production, and it is important in the maintenance of the natural resistance to certain bacterial, protozoal, and hematozoic infections (tuberculosis, malaria, *Bartonella*).

It is evident, from this brief statement of the structure and functions of the spleen, that enlargement of this organ may occur under a great variety of circumstances. The chief ones are listed in table 27.

Table 27

CHIEF CAUSES OF ENLARGEMENT OF THE SPLEEN

I. Infections:

- A. Acute splenic tumor of various systemic infections (typhoid, septicemia, infectious mononucleosis, various contagious diseases, etc.)
- B. Subacute infections such as subacute bacterial endocarditis
- C. Malaria
- D. Other parasitic infections (leishmaniasis, trypanosomiasis, schistosomiasis, etc.)
- E. Chronic diseases such as tuberculosis, syphilis (especially congenital), chronic "infectious" arthritis, histoplasmosis, etc.

II. Congestive splenomegaly ("Banti's disease," etc.)

III. "Hyperplastic" splenomegaly:

- A. Acute and chronic, frankly hemolytic anemias
  - B. Chronic anemias of various types (pernicious anemia, chronic hypochromic anemia, myelophthisic anemia, myelosclerosis, Mediterranean anemia, etc.)
  - C. Leukemia
  - D. Polycythemia vera
  - E. Thrombocytopenic purpura
- IV. "Infiltrative" splenomegaly (Gaucher's disease, Niemann-Pick disease, amyloidosis, etc.)
- V. Neoplasms and cysts:
- A. Benign neoplasms and cysts (hemangioma, parasitic cysts, etc.)
  - B. Lymphosarcoma, Hodgkin's disease, etc.

panied by enlargement of the spleen. Abscess of the spleen is rare.

Malaria is, perhaps, the most common cause of splenic enlargement when the world population is considered. Infection with other parasites which leads to splenic enlargement includes leishmaniasis, trypanosomiasis, and schistosomiasis. In kala-azar the spleen may be huge.

Primary tuberculous splenomegaly is extremely rare, but slight enlargement of the spleen accompanying a widespread tuberculous infection is by no means unusual. Splenomegaly may occur in connection with syphilis, especially congenital syphilis. Enlargement of this organ may also accompany the late stages of syphilis in association with gummas or amyloidosis. Chronic "infectious" arthritis and brucellosis are other chronic diseases which may be accompanied by splenic enlargement.

The vascularity of the spleen and its location in the portal bed make this organ liable to swelling as the result of increased venous pressure in that region. Such types of enlargement of the spleen can be classed under the general heading of "congestive splenomegaly," and include the syndromes known as "Banti's disease" and "splenic anemia," as well as the splenic enlargement which accompanies cirrhosis of the liver and thrombosis of the splenic or portal vein, and that which may be associated with cardiac failure.

The functions of the spleen in relation to the hemopoietic system result in enlargement of this organ when there is increased blood destruction (acute and chronic hemolytic anemias), or in the presence of chronic anemia of various types such as pernicious anemia, chronic hypochromic anemia, myelophthisic anemia, and "Mediterranean" anemia. Again, the spleen is enlarged, as a rule, in leukemia. In polycythemia vera splenomegaly is often encountered, and this finding helps to distinguish the primary disorder from secondary forms of polycythemia, where splenic enlargement is rare. The lymphatic hyperplasia which is associated with hyperthyroidism may be accompanied by splenomegaly. The spleen is also enlarged in conditions described under the names "primary splenic neutropenia" (p. 1212) and "primary splenic panhematopenia" (p. 1213).

Certain rare diseases such as Gaucher's disease and Niemann-Pick disease are characterized by splenic enlargement. In these conditions the swelling of the organ is probably due to the ex-

Of greatest frequency is the enlargement of the spleen which is seen in association with infections. The "acute splenic tumor" accompanying various systemic infections such as typhoid fever and septicemia are examples. Like lymph node enlargement, splenic enlargement is frequently encountered in various contagious diseases, and is often seen in infectious mononucleosis. Likewise, various subacute infections, notably bacterial endocarditis, are characteristically accom-

cessive storage of normal and abnormal metabolic products in the cells of the spleen.

Like other organs, the spleen may be enlarged as the consequence of the presence of neoplasms of various types. Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma, however, are far more common causes of splenomegaly than other types of new growth. Carcinoma is the most frequent type of metastatic tumor, but even this is extremely rare. Benign tumors which may involve the spleen include lymphangiomas and hemangiomas. Cysts of the spleen may be of parasitic origin or nonparasitic. Of the latter, those containing serous or hemorrhagic fluid and due to trauma are the most common. They can sometimes be identified roentgenographically because of calcification of the wall.

#### DIFFERENTIAL DIAGNOSIS OF SPLENOMEGLY

A thorough physical examination, together with the history and examination of the blood, will serve to differentiate many of the causes of splenomegaly which have been outlined. Sometimes additional procedures may be required, such as blood culture, sternal puncture, a roentgenogram of the chest, serologic tests including those for syphilis, liver function tests, and lymph node biopsy.

The absence of fever is more helpful in differential diagnosis here than is its presence, since most of the conditions which have been mentioned may be accompanied by fever. However, at times, as in malaria and in undulant fever, the characteristic temperature curve is very helpful in making the diagnosis. In the septicemias the splenic enlargement is, as a rule, obviously only a minor feature of the whole clinical picture. The exanthemas are recognized by the respective characteristic changes in the skin. In their absence the skin should be inspected carefully for evidence of the petechiae which may accompany acute leukemia, thrombocytopenic purpura, or myelophthisic anemia; the red petechiae occurring in crops together with the larger, slightly nodular and tender Osler nodes so characteristic of subacute bacterial endocarditis; the spider telangiectases which accompany long-standing liver diseases; or the plum-red "cyanosis" of polycythemia vera.

Moderate lymph node enlargement accom-

panying splenomegaly is seen in many infectious diseases as well as in leukemia, but an asymmetric enlargement should arouse suspicion of Hodgkin's disease or lymphosarcoma. Great enlargement of the lymph nodes is seen in the last-named conditions as well as in chronic leukemia, especially in the lymphocytic form. The discovery of icterus suggests hemolytic anemia as a cause, or, if there is little or no anemia and the splenic enlargement is only slight, infectious hepatitis. The splenomegaly associated with the Banti syndrome (congestive splenomegaly), and cirrhosis of the liver, is usually substantial in degree, and jaundice is not the rule under these circumstances. Malaria must be kept in mind among the causes of hemolytic anemia.

Lesions in the mucous membranes accompanying splenic enlargement are seen in measles (Koplik's spots), secondary syphilis (mucous patches), infectious mononucleosis (infection of the throat, tonsillar enlargement, sometimes signs of Vincent's angina), and acute leukemia (swollen, thickened gums which may be bleeding or purplish in color). In the leukemias, sternal tenderness may be quite pronounced.

The discovery of very great enlargement of the spleen tends to rule out the acute splenic tumor of various systemic infections, although sometimes the spleen may extend 4 to 6 em. below the costal margin in septicemia and in subacute bacterial endocarditis. Huge spleens are encountered in the chronic leukemias, in the Banti syndrome, in kala-azar, in schistosomiasis, in Gaucher's disease, in Hodgkin's disease and lymphosarcoma, in myelofibrosis, and in many instances of chronic hemolytic anemia, especially congenital hemolytic jaundice.

Examination of the blood may indicate at once the nature of the disorder, as in malaria, the frank leukemias, or infectious mononucleosis. The discovery of icterus will lead to a reticulocyte count, examination of the stools and urine for the products of blood destruction, an erythrocyte fragility test and other studies (see p. 1194) to rule out the various hemolytic anemias. The discovery of leukopenia should lead to the consideration of malaria, "aleukemic" leukemia, the Banti syndrome, typhoid fever, histoplasmosis, and leishmaniasis, but it must be kept in mind that the white cell count may sometimes be low also in infectious mononucleosis and in some cases of chronic hemolytic anemia. The demonstration

of thrombocytopenia, as well as prolonged bleeding time, poor clot retraction, and positive tourniquet test, is an important finding, for it suggests thrombocytopenic purpura. These changes may be observed also in acute leukemia, where, in addition, immature leukocytes would be found and anemia out of proportion to blood loss. Thrombocytopenia only very rarely accompanies infectious mononucleosis, and while present in other conditions such as pernicious anemia, chronic hypochromic anemia, chronic hemolytic anemias, myelophthisic anemia, the Banti syndrome, Hodgkin's disease, and the related lymph node disorders, it is rarely well marked in these diseases.

Sternal puncture may be very helpful if "aleukemic" leukemia, leishmaniasis, or Gaucher's disease is being considered seriously, for the characteristic cells or causative organisms may be demonstrated in this way. Sternal puncture does not often reveal malaria when the parasites have eluded careful study of the blood, but sometimes positive blood cultures for bacteria are obtained by this means when the usual method has failed.

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## Part II

# PHYSIOLOGIC CONSIDERATIONS

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## Section 1—Inheritance and Aging

# 25

## Inheritance of Human Disease

Frank H. Tyler

### Introduction

Simple Mendelian Inheritance—Dominant and Recessive

Sex-Linked Inheritance

Common Mechanisms of Human Inheritance

More Complex Mechanisms of Human Inheritance

### INTRODUCTION

Many disease processes, as well as many non-pathologic traits, are genetically determined. It is important for the physician to understand their pattern of occurrence, and it is often necessary for him to enlighten parents and potential parents of the probabilities of transmission of known traits to their offspring. Wise advice by the physician and intelligent decisions on the part of the patient about the desirability of offspring require intimate knowledge of the genetic patterns of inheritance and the variability of the disability to which the inheritance of a given trait may lead. Two brief examples will illustrate the problem.

Red-green blindness is a common finding in males as the result of the fact that it is a widely distributed trait which is inherited as a sex-linked recessive. It is always manifest in those male individuals who carry the trait, and it is transmitted only to daughters by the involved male. These daughters do not manifest the trait, although half of their male offspring may be red-green blind. This inherited abnormality leads to disability, however, only in very special circumstances where the ability to distinguish these colors is important.

On the other hand, myotonia dystrophica is a dominant trait of extreme variability. Parents with mild manifestations frequently have severely handicapped children. The presence of the trait is usually identifiable in adults. Those who do not show even minimal signs of the disorder may be reassured about the improbability of their transmitting the disorder, even though their siblings may manifest it.

It is important to emphasize, furthermore,

that the organism's response to any disease depends in part on a large group of constitutional factors which are genetically determined. For example, acute streptococcal pharyngitis is sometimes followed by rheumatic fever or glomerulonephritis. In some manner, which is not clear at present, the individual's response to the original infection is determined by certain constitutional factors, as well as by environmental circumstances. It follows that inheritance is important in many diseases, some of which manifest no obvious familial tendencies.

### SIMPLE MENDELIAN INHERITANCE—DOMINANT AND RECESSIVE

Mendel recognized the primary mechanism of inheritance in plants. Subsequent investigators have extended our knowledge until we now understand many of the patterns in animals and man, as well as in plants. Only the simplest genetic patterns can be outlined here. Many complex genetic mechanisms are no doubt also operative in man, but their study is made difficult by the fact that human families are usually small, the reproductive cycles are long, and critical matings are lacking.

In those genetically determined disorders in which the mechanism of the inheritance is understood, the probability of transmission of the characteristic to the offspring is predictable. In the simplest form of inheritance, only one site on the chromosome affects the trait, and the determiner at that location is called the *gene*. Only one gene can be present at a given site in a single chromosome, but the chromosomes occur in pairs, and thus there are two genes for each character (see table). The term *allelomorphs* refers to two or more genes which may occupy the same position on a chromosome (e.g., A, a, A' in the table). If both chromosomes of a pair contain the same gene (e.g., A, A), the organism is said to be

TABLE OF DIAGRAMMATIC REPRESENTATION OF THE THEORY OF MULTIPLE ALLELOMORPHS

A	A	a	a
B	B	B	B
C	C	C	C
D	D	D	D
<i>Homozygous Dominant</i>		<i>Homozygous Recessive</i>	
A	a	A	A'
B	B	B	B
C	C	C	C
D	D	D	D
<i>Heterozygous</i>		<i>Heterozygous</i>	

A pair of chromosomes is diagrammatically represented as chains of genes. In genetic notation the dominant gene is usually represented by a capital letter (e.g., A); the recessive allele of that gene is represented as a lower case letter (a). If more than two known alleles exist, other obviously related symbols are used to represent them (A').

Note that a given gene is always paired with the same gene or one of its alleles; that only two of a group of allelomorphs may be present in a single individual.

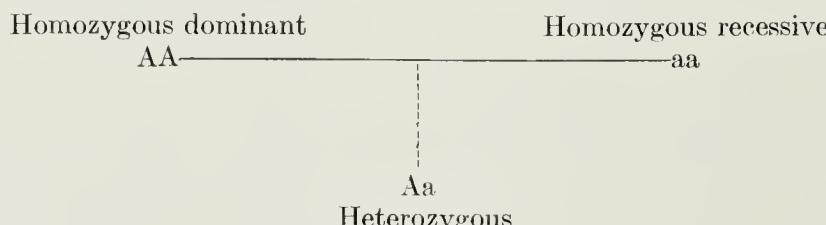
The heterozygous state is represented at the left in its usual form and at the right in a less common form in which an unusual allele (A') is associated with the common dominant allele.

homozygous with respect to that character, and the organism manifests the trait. If different allelomorphs are present (e.g., A, a), the organism is heterozygous. In such circumstances the

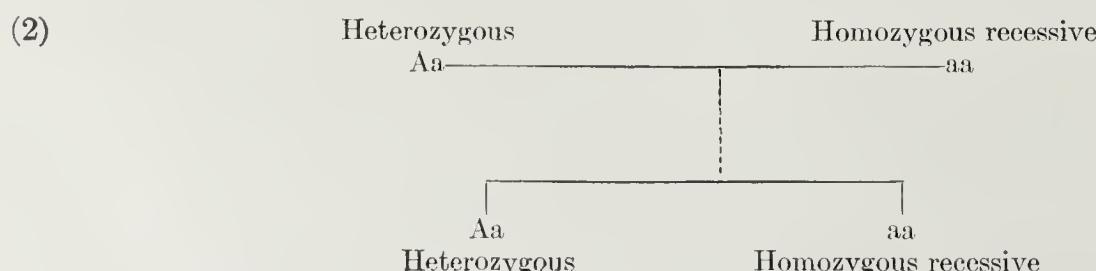
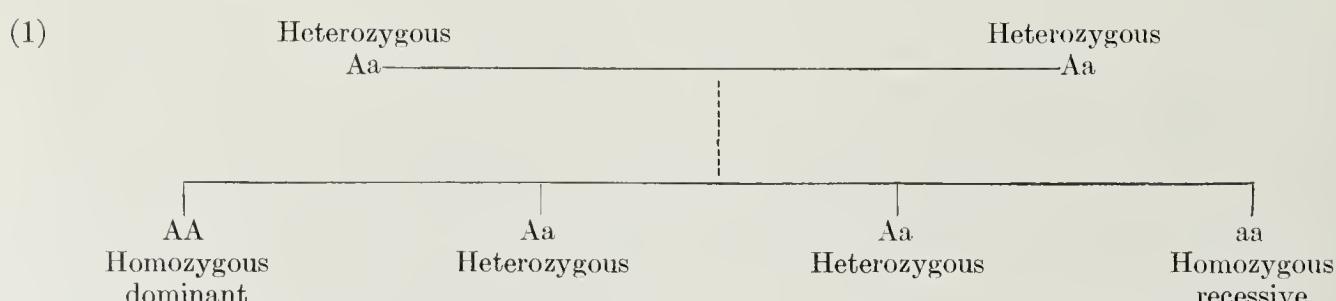
organism will manifest the characteristic of only one of the two allelomorphic genes, and that one is said to be *dominant*. The other is referred to as *recessive*.

The offspring of individuals both of whom are homozygous for a character regularly manifest that character unless a change in the gene (mutation) has occurred. Mutations are very rare. Where the parents are each homozygous for a different allelomorph, all of the offspring will be heterozygous, having received one of each pair of chromosomes from each parent. The offspring will manifest the characteristic of the gene which is dominant. If two heterozygous individuals reproduce, three quarters of the offspring will show the dominant characteristic (one homozygous dominant and two heterozygous dominants) and one quarter will show the recessive. It follows that recessives, when manifest, are always homozygous.

Thus, if we represent the dominant character by a capital "A" and the recessive character by a lower case "a," the mode of transmission would be as follows:



That is, all of the offspring will be heterozygous and will manifest the dominant trait. Other combinations may be similarly illustrated.

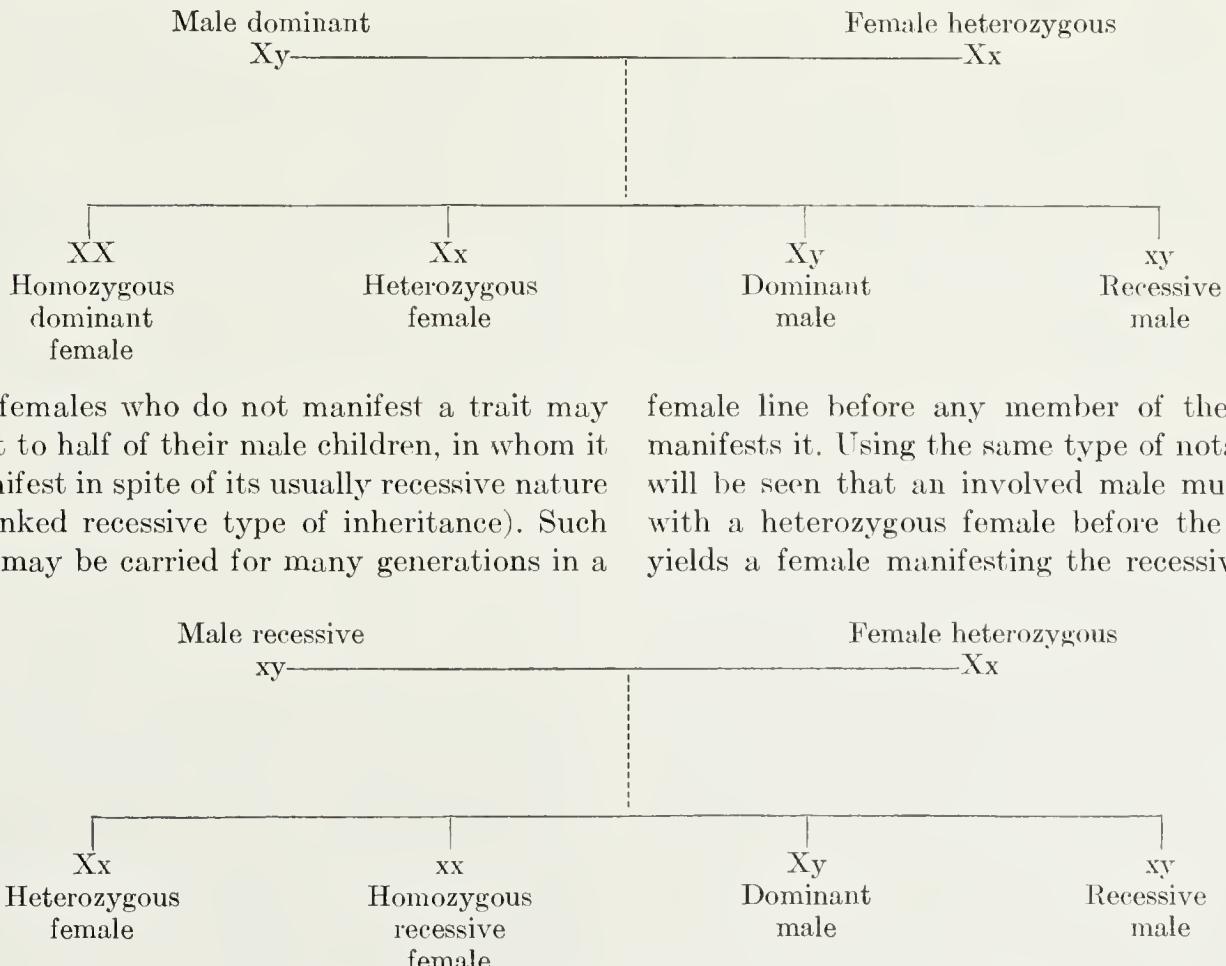


By chance distribution, half of the offspring will possess one dominant gene, but, because it is dominant, such offspring will manifest the character.

### SEX-LINKED INHERITANCE

One of the pairs of chromosomes (there are a total of 24 pairs in man) is unlike all the other pairs in that there is a nonfunctional<sup>1</sup> mate in

males. When the gene determining the inherited character lies in this pair of chromosomes, the so-called sex chromosomes, a special type of inheritance occurs which is called the sex-linked type. Because of the absence of one gene, even unpaired recessives are manifest. If we let *y* represent the nonfunctional sex chromosome, *X* the dominant, and *x* the recessive gene in the above scheme, the mode of inheritance is as follows:



Thus females who do not manifest a trait may pass it to half of their male children, in whom it is manifest in spite of its usually recessive nature (sex-linked recessive type of inheritance). Such traits may be carried for many generations in a

female line before any member of the family manifests it. Using the same type of notation, it will be seen that an involved male must mate with a heterozygous female before the mating yields a female manifesting the recessive trait.

Other combinations are easily worked out on these same patterns.

### COMMON MECHANISMS OF HUMAN INHERITANCE

Many human characters and certain diseases are inherited according to these principles. The majority of abnormal or disease characters which have been adequately studied are typical of the dominant type of inheritance; i.e., the abnormal gene is dominant and manifest when present. A smaller number of sex-linked recessives have

been clearly demonstrated; e.g., hemophilia, color blindness. Only a few abnormal recessive genes are known, although many may exist. It is apparent that it is difficult to recognize the human who is heterozygous for an abnormal recessive. As a consequence, a large number of observations is required in order to establish a character as a true recessive.

### MORE COMPLEX MECHANISMS OF HUMAN INHERITANCE

"Penetrance" of a genetic characteristic refers to the regularity with which a given genetically determined characteristic is manifest. Although a character may be dominant in the sense that it may be manifest in any individual who carries

<sup>1</sup> This is usually called the "y chromosome." Actually a few genes do occur on "y" chromosomes. They are of no clinical importance so far as is known at this time.

the single gene, certain other developmental or environmental factors may be required before it becomes manifest. If such factors are not regularly present, the penetrance of the trait is said to be incomplete. A related but different phenomenon is the inheritance of genetic determiners for disorders which do not become manifest until a certain stage of development is attained. Thus, facioscapulohumeral dystrophy cannot be identified in children, although it is completely penetrant in adults.

Human genetic traits may lead to varying degrees of manifestation in different individuals who have the same complement of primary genes for the trait. This occurs presumably as a result of other genetic and environmental factors which are different in the two individuals. This phenomenon is called *expressivity*, and may be consistent or extremely variable.

Dominance of some traits is not complete; that is, although a single gene may be manifest when present, the homozygous condition may lead to a different degree or type of expression. An example of this phenomenon is the probable relation of sickle-cell anemia to the trait for sickling which is found in many Negroes. The gene involved is apparently a dominant which might be represented as *Sk*. If the normal is designated as *sk*, the person who manifests the trait will have the complement of genes, *Sk sk*, while the patient with sickle-cell anemia will possess the genes *Sk Sk*. The normal person will have the homozygous recessive genes *sk sk*. Because patients with sickle-cell anemia seldom reproduce, nearly all patients with such anemia will be the result of the mating of two persons with the trait. However, such matings will produce offspring only one quarter of whom manifest sickle-cell anemia. The ratio may actually be lower than this because the homozygous state of

such incompletely dominant genes may not be compatible with survival even in intrauterine life, thus leading to a falsely low incidence of the anemia.

Sometimes a single characteristic is modified in its expression by many pairs of genes. These added genetic determiners may or may not be dependent on the presence of primary gene, and may either enhance, modify, or inhibit partially or completely the expression of the trait.

Some genes are known to have more than two allelomorphs, thus complicating the pattern of inheritance, because only two can be present in a given individual.

These complications have been well demonstrated in animal genetics, but their importance in human genetics is mainly to allow us to understand how certain diseases which are obviously familial in character but do not follow simple Mendelian laws may be genetically determined. The difficulties inherent in the study of human genetics are apparent on consideration. The difficulty which arises in proving such phenomena in human genetics stems from the rather small families with which we ordinarily deal and from the frequent inability to find satisfactory numbers of the critical matings on which statistically satisfactory analyses can be made. One error which is all too commonly found in such studies is the uncritical acceptance of family histories as given by poorly qualified observers. Actually, many of the inconsistencies disappear when careful clinical examination of both presumed normal and abnormal individuals is made by competent investigators.

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# 26

## Aging and Involution

William Dock

Definition and General Considerations  
Aging and the Vascular System  
Manifestations of Involution

### DEFINITION AND GENERAL CONSIDERATIONS

Aging includes all the acquired changes which require time for their development, and involutional changes which are as much a part of mammalian life as the autumnal involution of the leaves of deciduous trees. Accumulations of fat, of cholesterol in the arteries or gallbladder, of chalk in the cartilages, all require time; hence, they are more advanced in the aged than in the young. Changes in the subdeltoid tendon sheath or about the vertebral bodies occur from stress—the oftener repeated the stress, the more marked the changes. Hence old people show more change than younger ones. Involution probably also plays a part in altering the composition of the tissue in all these cases, but age and repeated exposure to a noxious influence are also necessary to evoke clinical evidence of impaired function.

Aging, then, may be defined as the sum of the losses of function and structure and of the callousities, scars, and nodular hyperplasias due to "wear and tear" and to involution. "Wear and tear" includes trauma; infection; overstimulation by emotional, dietary, or other abuses; dietary inadequacies; exposure to inclement weather; exhausting activity; and so on. Changes in metabolism not due to such abuses or overstimulation must be ascribed to involution, if it occurs in a large proportion of members of certain families after the age of maturity. The effects of such involution may not become apparent under ideal conditions. Thus diabetes may not become manifest if the population is found to live on a low-calorie diet. One interpretation of this would be that diabetes is due to dietary excess, even though it never develops in most of those who live on faulty diets. We accept the other view, that pernicious anemia, gout, and diabetes developing after maturity are due to innate involutional faults.

The boundary between what one chooses to classify as involutional and abiotrophic is arbitrary. If involutional means "the usual or expected change occurring with age," and abiotrophic means "the exceptional progressive anatomic and functional loss which may occur at any time during development or senescence," then gout and diabetes, idiopathic Parkinson's and pernicious anemia, are all abiotrophies, along with, perhaps, amyotrophic lateral sclerosis, Alzheimer's psychosis, and progressive muscular atrophy. In the future we may expect to learn more about the genetics and the external factors which control these disorders. Then we may include in aging many cases of Paget's disease, Graves's disease, myxedema, etc., which are now called idiopathic, or we may narrow aging to those disorders which are inevitably present in all men or women who reach the age of 70, or 90. Thus baldness and even graying of hair would be classified as abiotrophies, because they do not invariably manifest themselves before 90.

### AGING AND THE VASCULAR SYSTEM

Even in the aged, the vascular bed is able to grow and to adapt itself to circulatory needs. Tumors in the aged become well vascularized, and arteries leading to them enlarge strikingly. Only when the arterial lumen is severely encroached on by atheroma does the vascular supply fail in the organs and brain of the aged. Inflammatory disease also may lead to vascular inadequacy at any age; and in the coronary arteries of the heart, atheroma may cause trouble soon after puberty in patients with very high blood cholesterol levels. The vessels of the legs also may suffer soon after maturity in such patients, and in severe hypertension, bilaterally symmetric and diffuse lesions of small arteries may become evident in the brain, retina, and kidneys, even before maturity. In the absence of initial unilateral lesions in the normotensive, and in the absence of retinal lesions in the hypertensive, it is never safe to as-

cribe changes in memory, judgment, and originality to cerebral arteriosclerosis. In the absence of angina or evidence of a myocardial infarct, it is equally unsafe to ascribe cardiac failure to arteriosclerosis. In the heart there is only coronary atherosclerosis involving the large epicardial branches; even in hypertension the arterioles in the myocardium usually remain unaltered.

The most vigorous objection must be registered to the notion that men are "as old as their arteries." Men may die of coronary atherosclerosis before they are old enough to vote; these arteries are diseased and not "old." Temporal arteries may stand out as large, tortuous vessels in men under 30, yet at 90 the same men may be alert and in good health. This is due to fibrosis with ectasia, a clinically unimportant vascular involution. Men are as old as their skins, their scalps, their cerebral cortices, and all their other tissues. Since aging shows up most strikingly in the skin and brain, even when these have excellent vasculature, a man might be said to be no older than his ectoderm. He is vulnerable to death from a congenital weakness in 5 mm. of his circle of Willis, or from atheroma in 1 cm. of one coronary artery.

### MANIFESTATIONS OF INVOLUTION

The tissues of the body undergo aging at very different rates in different organs, species, and individuals. To some degree the rates are influenced by environment, nutrition, infection, trauma, or abuse, but even these influences are minimal—great variations in aging of specific tissues are obvious in individuals and in families as well as in species. Grizzly bears and gorillas have graying of the hair on reaching maturity; other bears and primates have none at advanced ages; some families turn white in the thirties, others not until after seventy. Wrinkling of the face and neck may occur early in members of families who become neither bald nor gray until old age. Pulmonary elastic fibers may age and emphysema become troublesome in men whose elastica ages slowly in the skin or the arteries.

The pattern of graying, baldness, and coarsening of the hair of the face, nostrils, and ears shows clearly how atrophy may proceed in one area while hypertrophy is occurring in another. Focal hyperplasia in the presence of atrophy is a commonplace of aging of the skin, breast, prostate, and thyroid, and in the gastric mucosa. Sym-

metric degeneration of neurons may occur in certain parts of the cerebral cortex, or the cerebellum, or the substantia nigra, while preservation of neurons in adjacent regions is still excellent. This is often incorrectly ascribed to vascular disease; in the scalp no loss of vascularity is necessary to cause baldness or graying, and in the brain no local ischemia precedes the symmetrical loss of neurons. In many organs, involutorial atrophy precedes disuse atrophy of the vascular bed, which then undergoes secondary degenerative changes.

Physiologic involution, such as that in the lens and uveal tract which causes loss of near vision (presbyopia or the "elder's eye"), may be associated with minimal histologic change. Anatomic involution, such as disseminated cortical atrophy of the frontoparietal regions, may be grossly striking, with almost no functional loss. In the former type, chemical systems age and wear out, but cell structure is little altered; in the latter, cells disappear but the effect is minimal because vital activity is carried on in adequate fashion by the remaining tissue. The aging heart recovers less rapidly during diastole than does the young heart; consequently, heart failure occurs under conditions which a few decades earlier did not even cause transient dilatation. In all such cases, the diagnosis of involution is made from two sets of facts. The mature patient may become senile in certain tissues at almost any age, and, therefore, maturity is one essential datum. The other is the demonstrated absence of infections or metabolic or vascular disorders capable of accounting for the phenomenon in question. Thus pellagra may simulate involution of the brain, beriberi simulate involution of the heart, and syphilitic aortitis simulate senile dilatation and elongation of the aorta. Much the most convincing evidence for involutorial causation is a familial pattern of occurrence, and the widespread occurrence of similar disorders in aging mammals of various species.

Fortunately, many involutorial losses are readily corrected—the hair can be dyed, the long hairs in the ears and nostrils clipped, the bald scalp can bewigged with a toupee. Others are turned to assets: the faulty memory of the aged and their deafness excuse much and spare effort and annoyance. Finally, some chemical involutions can be corrected. Those which cause pernicious anemia and combined cord lesions are ef-

fectively treated with liver extract; senile heart failure is usually responsive to digitalis; presbyopia is easily corrected by eyeglasses, and so on. Some physicians hesitate to diagnose disease as due to involution until after three score years and ten, or avoid this because it suggests an incurable disorder. Both of these reasons are incorrect. Many involutions, like presbyopia, can be demonstrated in larval stages in the twenties in nearly everyone; others, like baldness and the disorders of urate metabolism called gout, are manifest before 40, in a very appreciable percentage of all those finally recognized; and many involutions, after rapid progress for a few years, become arrested and often compensated.

The involution of greatest importance to society and to the physician is that of the central nervous system. Anatomically, this is characterized by loss of neurons, which is demonstrable in the spinal cords and brains of mice, rats, and men. Loss of motor neurons decreases the fiber count of the spinal nerves and probably contributes to the loss of agility and athletic prowess, with sustained capacity for prolonged heavy loads of work, which is typical of middle and old

age. Loss of neurons in the basal ganglia accounts for tremor, rigidity, and even full-blown clinical disorders such as idiopathic Parkinsonism.

But most important of all is the loss of cortical neurons which diminishes the acuteness of observation, and when severe leads to the apathy, the irritability, the stolidity and garrulousness, the overly great concern for minutiae, and the loss of concern about essentials which are characteristics of senile psychoses, and of many older people merely regarded as eccentric, or bureaucratic. Older patients' histories are notoriously undependable. For every man or woman in whom "old experience do attain to something like prophetic strain," there are half a dozen in the asylums, and several score who "ain't what they used to be." It is the physician's function to detect the remediable disorders, such as brain tumor, pellagra, or myxedema, which masquerade as senile behavior, and to do what is possible to secure maximum comfort and effectiveness from the waning powers of aging men and women. Nothing is gained by refusal to recognize the fact that all men age and die, and that involution sets in with maturity, not in old age.



27

Principles of Neoplasia

William Dock

Nature of Neoplasms  
Etiology of Neoplasms  
Growth and Effects of Benign Tumors  
Growth of Cancer  
Detection of Cancer  
Management of Cancer

**NATURE OF NEOPLASMS**

Cancers and benign neoplasms arise from the cells of the body and behave as though they were mutants with an impaired sensitivity to the organizing influences of adjacent cells, and with growth rates greater than those of adjacent cells of the organ from which they were derived. Benign neoplasms still respond to the organizing influences which maintain the boundaries between ectodermal, mesodermal, and endodermal tissues, or between various types of cells in tissues of mixed structure. Cancers ignore these influences and hence invade and metastasize. In structure and in metabolic and growth patterns, neoplasms depart more or less from the tissues from which they are derived. In general, the more rapid the growth and the greater the invasiveness, the more the tumor resembles embryonal rather than mature tissues; it has become undifferentiated or anaplastic. Yet some cancers of the thyroid growing in distant sites retain the structural, metabolic, and hormonal peculiarities of the adult tissue of the organ from which they arise. On the other hand, the pathologist does not hesitate to classify as cancer lesions which are sharply localized at their sites of origin, if they have histologic features usually seen in cancer.

Neoplasms exert organizing influences on adjacent tissue. They evoke the growth of vascular and lymph channels, and of supporting fibroblastic collagenous tissue. In some cases epithelial tumors evoke growth of adenoid lymphatic tissue. The cancers which develop in the nasopharynx may elicit such a massive lymphoid response as to be called lymphoepitheliomas. Neoplasms, like individuals, can be classified and

tend to run "true to form," structure carrying with it behavioral pattern. Yet each neoplasm is as original and specific as each person. Some neoplasms undergo progressive changes in structure and behavior, the more anaplastic areas outgrowing the more highly differentiated parts of the tumor.

Cancer cells invade just as the trophoblasts of the placenta invade the uterus, and undoubtedly in both cases many cells enter the lymphatic system and the blood stream. The trophoblasts proliferate only near the placental site and all die off as pregnancy ends, save in rare cases of chorioepithelioma. Ability to grow in the lymphatic channels characterizes some epithelial cancers. Ability to grow in distant sites is characteristic of malignancy in general. Usually a cancer is most discriminating in its selection of a suitable soil, and thus shows a preferential distribution of metastases. Spleen, voluntary muscle, and myocardium seem to supply poor soil; bone, liver, brain, and adrenal, on the other hand, have far more metastases than can be accounted for merely by the proportion of blood flowing through them. But each cancer has its own pattern of spread; one cancer of the stomach may flourish only in the liver, another only in the lungs.

Many neoplasms undergo spontaneous necrosis, partly because of vascular defects, but partly because the cells mature and die in places where desquamation is no longer possible, or at rates which make orderly cytolysis impossible. Because of necrosis, or because of production of abnormal metabolites, many neoplasms cause systemic reactions, sometimes with fever, leukocytosis, and rapid erythrocyte sedimentation rates; at other times, only with fatigability, apathy, anorexia, or "unexplained" anemia or weight loss. Cancer may lead to a wasting disease, or to a depressive psychotic state, before it

causes local symptoms. These effects are ascribed to the products of cell necrosis, and may precede fever, leukocytosis, or fast sedimentation of red corpuscles. Where bleeding does not occur, anemia in cancer is ascribed to such a toxic action, similar to that causing anemia of infections or of uremia. The anemia also may be due to widespread bone marrow invasion.

### ETIOLOGY OF NEOPLASMS

It has been stated above that neoplasms behave as if they arose from somatic cells undergoing mutation and giving rise to generations of abnormal cells. That cancer does actually represent somatic mutation is a thesis warmly defended by some investigators and bitterly rejected by others. It will be recalled that germ cell mutation, leading to generations of creatures different from the standard hereditary pattern, or to individuals so abnormal that reproduction or even normal life span is impossible, occurs spontaneously in a population of fruit flies, microbes, plants, or mice, and that the frequency of mutation can be increased by x-ray, ultraviolet radiation, or even by specific forms of chemotherapy applied to the colony.

One reason for not accepting the mutation theory is that both cytologic and chemical study of tissues exposed to chemical carcinogens indicates a gradual rather than an abrupt change from normal to cancerous characteristics. On the other hand, no one denies the fact that cancer cells, in the tissues, in tissue culture outside the body, or transplanted to the anterior chamber of the eye of another species, maintain their peculiarities of structure and of chemical function indefinitely. They breed true, and they differ from the parent tissue just as a mutant strain of dogs or cats breeds true and differs from other strains regardless of environment.

That the cells of the soma may undergo abrupt changes in chromosomal structure and hence in behavior, similar to those constantly occurring in the germ cells, has not been proved. This possibility is one which some investigators accept as quite reasonable, while others deny it with religious fervor. Such mutations would usually lead to cell death, or to dysfunction in one cell and its offspring. This would explain many of the focal changes in cell function which the pathologist speaks of as involution: "liver spots" and keratoses on the skin, islands of intestinal mucosae in

the pyloric mucous membrane, Paget's disease of bone, etc. If the mutation led to increased growth rate and loss of responsiveness to organizers from adjacent cells, it would manifest itself as a neoplasm. The high incidence of leukemia and neoplasm in men and mice exposed to x-rays, and the fact that x-rays are the most effective agents in increasing the rate of spontaneous genetic mutation in fruit flies and in molds such as *Penicillium*, is one of the strongest evidences that neoplasms are manifestations of mutation in somatic cells.

One form of cancer—retinoblastoma—occurs with a familial, hereditary pattern which follows Mendelian laws. It affects first one and then the other eye of the infant or child. Hereditary predisposition to spontaneous cancer, or to cancer induction, is apparent in man, in other mammals, and in cancers of other vertebrates, and even in plants. Tar induces skin cancer in mice regularly, in dogs rarely; in monkeys no tar cancers have been evoked. Tar cancers were first noted in the scrota of chimney sweeps, often appearing in early life, so that man here is more like a mouse than a monkey. Dogs get bladder cancer from naphthylamine; mice do not. Obviously, then, heredity alone causes cancer in rare cases, or acts as a predisposing cause in many. Nothing is known of the cause of the prepubertal cancers such as mixed renal tumor (Wilms's tumor) which show no hereditary background, but perhaps these and the gonadal mixed tumors arise in congenitally aberrant tissue. Sarcomas of all sorts, including those of bone, are rare, but their incidence prior to puberty is relatively high. After puberty, cancer becomes more frequent. In some cases occupational exposure to x-rays or to sunlight, or carcinogenic agents, may play a part, in others involutional change in the tissue precedes cancer, but in most cases no local cause is apparent. In the aged, cancer occurs outstandingly in organs structurally altered by involutional change, and notably in sex glands, skin, and stomach. Paget's osteitis, apparently an involutional disorder of bone much like senile keratosis of skin, predisposes to bone sarcoma.

It cannot be stated too strongly that we know far more about the etiology of cancer than we do about most diseases. For example, typhoid fever and infectious hepatitis have never been produced experimentally in mammals, while cancers and leukemias of all types have been experi-

mentally evoked in various mammals. In the rat, cancers of the skin, breast, thyroid, pancreas, liver, and bladder, various sarcomas, and leukemia have been produced repeatedly in strains with very low spontaneous cancer rates by feeding aminofluorene, a simple coal-tar derivative, in doses which have no other effect on growth or health of the animals. All of us are constantly exposed to cosmic radiation, which has been shown to raise the rate of spontaneous mutation in fruit flies, and many of us are exposed to ultraviolet light of high intensity, or to proved chemical carcinogens. We do not know why most people have a trivial local lesion followed by high immunity when they are infected by the tubercle bacilli to which all urban dwellers are exposed, while a few people develop real illness or die of tuberculosis. Similar mystery surrounds the pneumonias, arthritides, and countless other common inflammatory diseases. Those simple souls who are satisfied when a pathogen is proved for a given suppurative or granulomatous lesion, should be satisfied with our knowledge of cancer. We have half a dozen proved cancer pathogens, quite different in nature, just as we now have, for the granulomas which Virchow considered a pathologic entity, such diverse causes as *Mycobacterium tuberculosis*, *Treponema pallidum*, the virus of lymphogranuloma venereum, *Coccidioides immitis*, and beryllium dust. The pathogenesis of all these diseases, and of cancer, is ready for further study in the human population and in the experimental animal. All are easily available for experimental study by biochemists, geneticists, and other students of fundamental aspects of life, for the pathogens have been defined clearly by the pathologists.

A number of virus-evoked cancers have been observed and transmitted by ultrafiltrates in birds, and one such cancer in mice. So far, none has been detected in man. Viruses which cause simple warts in the ears of wild cottontail rabbits evoke true cancers in domestic rabbits, but similar infections causing the common verruca of children's fingers, or mouth papillomas in dogs, never lead to cancer. The mouse cancer, transmitted by ultrafiltrable virus, causes no breast papilloma in most of the mice; it remains latent in the breast, like herpes virus in our mouths, until it causes a cancer. Similar situations may well be proved in other mammals, and perhaps in some cancers of man. But it seems as unwise

to assume that any human neoplasm is due to a virus infection as to assume that it is due to aminofluorene or to roentgen rays, merely because these can act as carcinogens. Mycobacteria, treponemes, and the virus of lymphogranuloma venereum all evoke tissue reactions of granulomatous character scarcely distinguishable by the histologist. In the same way, histologically identical cancers may be evoked by very different etiologic agents.

### GROWTH AND EFFECTS OF BENIGN TUMORS

Some benign tumors act much like echinococcus cysts or foreign bodies. They are walled-off lumps which may be annoying cosmetically, or by interfering with organic function. Some of these in the stomach or uterus may ulcerate and bleed. Some benign tumors destroy much adjacent tissue by pressure, and grow into the space formerly occupied by other organs. This differs from the invasion by cancer, just as immigrants gradually replacing "old families" in a city differ from immigrants who drive out natives and take over their lands by force.

Other benign tumors have endocrine or hormonal effects, some relatively readily understood, as when parathyroid adenomas raise blood calcium; others most obscure, as when thymomas occur in myasthenia gravis, or when ovarian fibroma evokes hydrothorax without lowering plasma protein or elevating venous pressure. Being alert to the possibility that rare benign tumors of endocrine glands may produce such effects, the physician is prepared to detect them and have them removed, thus ending a chronic disabling illness.

Two common disorders of advancing years—nodular goiter and prostatic hypertrophy—probably represent multiple benign adenomas of these glands, but no one can define clearly where nodular hyperplasia ends and adenomatosis begins. These adenomas usually are not enzyme- nor hormone-producing, the prostatic "hyperplasia" does not raise the plasma acid phosphatase as do many prostatic cancers, and most patients with nodular goiter do not have hyperthyroidism. Yet these benign growths have often been fatal because of compression of the trachea or the urethra. Carcinoma in situ can be found at autopsy or operation in 5 to 8 per cent of such thyroid glands, and in more than 50 per cent of the

prostates of men over 60, but clinical cancer in these glands is not so frequent that thyroideectomy or prostatectomy can be recommended merely to remove cancer *in situ*, or common pre-cancerous foci. On the other hand, cancer develops so often in the multiple polyposis of the colon occurring in young adults, that colectomy seems justified. Benign tumors, then, may be removed either for relief of local dysfunction, for relief from endocrine or distant effects, or because of the statistical evidence that cancer is more likely to supervene than illness or death resulting from resection of the organ.

### GROWTH OF CANCER

Clinical experience teaches us that most sarcomas grow rapidly, and recur soon after resection if they are not wholly removed in time. Carcinomas show an extraordinary variability in the length of time during which they are local histologic lesions. After a breast resection, even before x-ray treatment was used, years or even a decade might pass before a small recurrence in the scar became apparent. As noted above, chance finding of cancer *in situ*, in certain glands of elderly people, is so frequent in relation to clinical disease that a long latency between onset and clinical signs of disease must be assumed. Yet some cancers recur locally soon after a thorough resection, and many of them metastasize widely before the local growth causes any trouble or is large enough to be palpated or seen by x-ray. Even in the leukemias, Hodgkin's disease, and myeloma (which usually are widespread before the patient is aware of any illness), exceptions occur with local disease in bone, or in skin—mycosis fungoides—causing trouble years before generalization is apparent.

Sarcomas usually are apparent locally before metastases occur, but even when a periosteal pain in the tibia leads to biopsy and amputation in a few days or weeks, multiple lung nodules may cause death within the year. Because of the great variation in behavior of tumors in any given site, or even of similar histologic structure, it is essential that the physician think of cancer early and always, that he should not defer definitive diagnosis where this may lead to operation, and that he regard a small group of "five-year cures" as more significant than the many cases whose lives are already doomed when the first symptom appears. Roentgen therapy too offers its best chance

for prolonging life in cases recognized early, and this is also true of hormonal or chemotherapeutic management of certain types of cancer or leukemia.

### DETECTION OF CANCER

Case finding in cancer has proved not to be worth while in those who feel well and are not aware of any lump or sore on their bodies. While periodic checkup on blood pressure, urine, and chest roentgenograms are simple enough to be feasible, and vaginal smear study may enter the same realm shortly, the tests for early cancer of the stomach and colon never will be as simple, nor will cancer always be detectable before metastasis, even if these tests are done. Recognition of early cancer requires alertness on the part of both the patient and the physician. The patient should consult his physician within the first weeks after a new symptom establishes itself. The physician should not only carry out a thorough initial examination but should continue to repeat the necessary tests until cancer is detected, or the duration of symptoms without cancer rules out this explanation of chronic illness.

Detectable early cancers are missed because doctors are not suspicious of cancer, or because they allow a negative study early in the course to lull suspicion, and repeat the study only when it is too late. This applies with great force to roentgen study. If a symptom justifies one roentgen study, and persists unexplained, the study should be repeated, first at two-month and then at six-month intervals, until the physician knows that an early lesion is not being missed. Physicians are accustomed to repeat their examinations at costs to the patient far below those charged for the initial study. Laboratory work and roentgen examinations remain just as expensive when repeated. This is unfortunate not only for the patient but also for the pathologist or radiologist who has a negative finding, and much later a strongly positive one, without the opportunity to see the earliest transition and thus learn how to recognize early lesions.

In any program for cancer detection in its early stages, cytologic diagnosis must be stressed. Sternal punctate, examined by an experienced observer, may show cancer cells when there is no radiologic or hematologic evidence of cancer. Marrow from other sites, and especially from the spinous processes and the iliac crest, may show

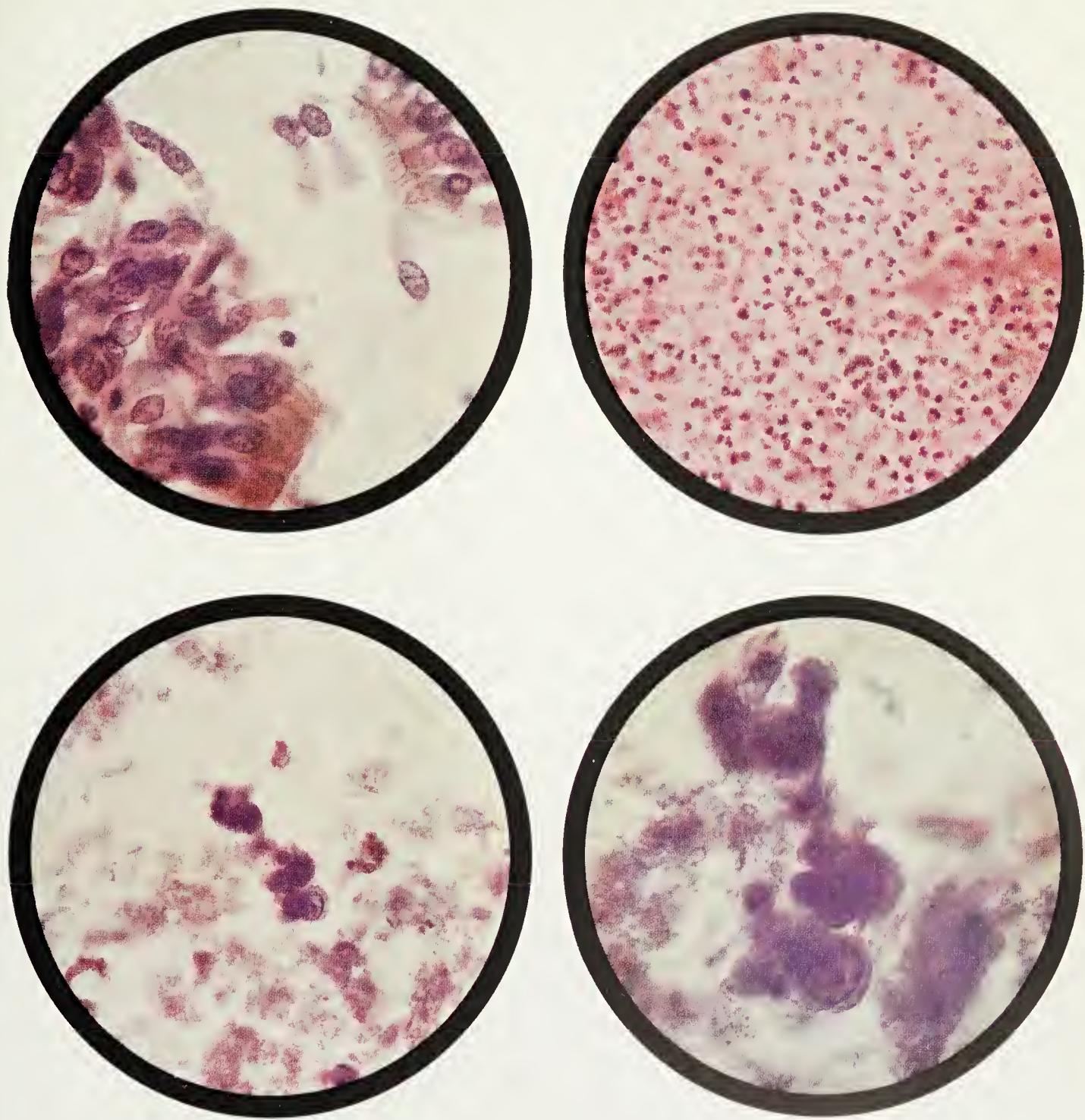


PLATE I

Sputum stained according to the Papanicolaou technic. (*Upper left*) Normal ciliated cells of the bronchial mucosa. Smear prepared from a bronchial aspiration ( $\times 375$ ). (*Upper right*) Smear of a bronchial washing from a case of abscess of the lung. It shows numerous inflammatory cells ( $\times 125$ ).

(*Lower*) Clusters of malignant cells from a case of carcinoma of the lungs. Note the large nucleoli and irregular pattern. The smear was prepared from a bronchial washing. (*Lower left*,  $\times 375$ ; *lower right*,  $\times 700$ .)

(Courtesy, Dr. George Papanicolaou.)



such cells when sternal marrow is still normal. Needle biopsy of the liver, of the lymph nodes, and of lumps in the breast, thyroid, prostate, or other sites, also is valuable in making early diagnosis. Papanicolaou technic, the use of properly fixed and stained smears from the genitalia or nasopharynx, gastric or duodenal washings, sputum or secretions obtained by bronchoscopy, is also of great value in detecting cancer at an early and perhaps a curable stage. With all of these cytologic technics, experience in the examiner, proper handling of material, and repetition of doubtful tests, or of negative tests with persistent unexplained signs or symptoms, is essential in order to avoid false positives, to make early diagnoses, and to prevent discrediting a method which is valuable when correctly used.

Every experienced physician has his own list of presenting symptoms and of incidental symptoms and findings which lead him to consider cancer, and to keep on thinking of it and searching for it month after month if the finding is persistent and unexplained. First, perhaps, would come "issue of blood" from any orifice, except cyclical endometrial bleeding. A bleeding nipple, in a man or woman, is presumably cancer, but so also is a bleeding rectum, for in both instances cancer is the most important although not the most frequent of the common causes. Lumps anywhere on the body, and sores about the mouth, progressive hoarseness, anorexia, change in bowel habit, unfamiliar colicky abdominal pain, the dull vague bone ache which is distressing even at rest, the new dry cough or the aggravated "cigarette cough"—all these are familiar as first signs of cancer, imitating common complaints of other patients in whom the duration of such disorders makes cancer highly improbable. Inguinal or axillary adenopathy may be the first symptom of malignant melanoma; cervical masses may be due to hidden cancer in the nasopharynx, paranasal, or pyriform sinus. Trivial dysuria may precede hematuria in bladder cancer, fleeting chest pain may precede pleural effusion or brachial plexus and stellate ganglion signs in lung cancer, yet similar pains are very common in people with no significant organic disease.

In the middle-aged, and even in the young, cerebral symptoms due to primary or secondary growths may be passed off as of emotional or arteriosclerotic origin. Even dysarthria or aphasia, if transient, is often dismissed and the pa-

tient not even kept under observation, with orders to report any return of symptoms or new disorders. Indigestion also is often ascribed to obvious psychogenic elements when it is the first evidence of leukemia or cancer. The apathy, lack of energy, or actual depression in cancer, especially with silent gastric or pancreatic lesions, has resulted in electroshock therapy or analytic interviews, and once a psychiatric diagnosis is made, all chance of early recognition of cancer may have been destroyed. Weight loss in cancer may occur without fever or anorexia, because some dulling of interest in life makes the patient unaware of his reduced appetite. A common minor complaint—unpleasant taste in the mouth day after day—may also be the only symptom reported by a patient with cancer of the upper gastrointestinal tract. Bouts of partial intestinal obstruction, clearing up after a few hours of colic and nausea, may be the only symptom for some months in cancer of the colon, and each time the patient or his wife will know just which item of diet caused the trouble. "Something he ate" could be put on the headstone of many a cancer victim.

Particularly suspect is the patient who comes for fatigability and is found to have a mild anemia. It is surprising how little distress occurs when the anemia of the classic blood dyscrasias is above the 8 Gm. % (55 per cent) hemoglobin level. In cancer, levels of 8 to 11 Gm. may be enough to bring sallow and weary patients in for help. Uremia, often latent in pyelonephritis and prostatitis, has a similar effect, and also causes anorexia and anemia. Sternal puncture is essential in all cases where the cause of anemia is not apparent, for multiple myeloma and bone cancer are often missed by several successive observers before the marrow smear is made.

The insidious onset of cancer, simulating functional disease, old age, or malnutrition, has been noted above. In another group of cases, biliary disease or hepatitis may be simulated; in a third, chronic infection with fever, tenderness, and leukocytosis. Another group simulates brucellosis, subacute endocarditis, or periarteritis by having purpuric or thrombotic accidents. Cancers of the pancreas may cause migratory phlebitis and even bland endocarditis with emboli. Meigs's ovarian fibroma, causing hydrothorax, and pleural cancer may masquerade for months as tuberculous pleurisy. Epicardial cancer, or the rare myocar-

dial metastasis, may mimic myocardial infarct, with typical electrocardiograms. On the other hand, syphilitic hepar lobatum with fever and ascites, and diffuse amyloid disease, have more than once been mistaken for cancer of the abdominal viscera with liver involvement. With some neoplasms, as with chronic granulomas, symptoms may be relatively constant, and some patients become more disturbed, others more accustomed to and less conscious of them, as the dysfunction persists day after day. In other patients, symptoms may be recurrent, each remission making the patient more hopeful, and each relapse more concerned. More frequently, however, conditions deteriorate week by week; new symptoms appear; old ones become more distressing. The physician must remain on guard in any case where symptoms persist or progress with no satisfactory explanation. He may well keep in mind the bitter comment of the lifelong neurotic, when his doctor finally discovered a high acid phosphatase after pooh-poohing his "aching back" for nearly a year, "Well, I suppose even we neurotics have to die from something sometime!"

While hope is entertained for dependable serologic tests for cancer, which will make possible early separation of those with neoplasms from those with other conditions, it seems possible that the infinite variety of cancer will make this a difficult problem. Early diagnosis, with minimal discomfort, worry, and expense in reaching a diagnosis, now calls for a high level of medical art and scientific training.

#### MANAGEMENT OF CANCER

Spontaneous remissions of the growth of human cancers, or remissions in the intoxication and pain, are not rare even in cases receiving only palliative treatment. Remissions of symptoms and pain occur with every type of treatment introduced by investigators or by charlatans, but actual regression and complete recovery is extremely rare except in patients treated by radical surgical procedures, or by radiation. Even now, no one speaks of cures, but only of the patients free of recurrence one, two, or five years after treatment. Only the per cent of "five-year cures" is used as an index of effectiveness of therapy.

While improved therapy for cancer is being developed, it requires great optimism to believe

that such cures for late cancers of all sorts will be numerous. Embryonal tissue is much like cancer, but after centuries of search, no safe and effective abortifacient has been found, capable of destroying the embryo without injury to the mother. Drugs with very high organ specificity are known, and the cancer problem is not, like perpetual motion, inherently insoluble. A safe chemotherapeutic agent for cancer almost certainly will prove an effective abortifacient as well. Early recognition, prompt use of methods now known to be effective, and holding out hope that better methods may be developed within the survival time of any given case make life more endurable for cancer patients today than it has ever been in the past, except for those in the hands of charlatans who keep them and their families convinced that recovery is certain up to the hour of death.

Because of the variable course of treated and untreated cancer, prognosis should be most guarded and diagnosis clarified to patients and relatives, so that the needed surgical or other therapy will be accepted without invoking certain death as imminent. It is wise to point out that one cannot be certain of the incurability, which is, from the layman's standpoint, the final proof of the "cancerous" nature of a lesion, even in a biopsied case. Often one must point out that leukemia includes cases dying of other causes after years of comparatively good health, as well as the acute leukemias so harrowingly described in the newspapers.

Where operative cure cannot be offered, or when cancer persists in spite of surgery, roentgen therapy should be used until it is obvious that the "cure is worse than the disease." Ideally, such therapy would be in institutes or clinics where the most effective and least harmful therapy can be given by experts with no financial or doctrinaire bias to roentgen therapy with the tube, to radium, or to active isotopes, but with all types of therapy available. Chemotherapy or hormonal therapy may be selected when roentgen therapy fails, or where a specific neoplasm makes such a choice statistically preferable. Thus urethane may be the preferred treatment for myelogenous leukemia, or stilbestrol for prostatic cancer of bone.

The patient with cancer should be encouraged to continue his work or his hobbies as long as possible; his morale and hope should be sustained by every wile short of chicanery; his nutrition

should be kept up and transfusions used liberally, as long as he is able to maintain an active interest in living. Some physicians believe that he should learn to endure pain, with the hope that it may lessen, rather than be put on narcotics with the impression that it is hopeless and he might just as well become an addict. Acetylsalicylate, phenobarbital, and alcohol are of value in this phase of management. Nerve block, or tract section in the cord, may be necessary in some cases; in others, frontal lobotomy may be the preferred management for depression and pain.

At present, hopes are high and morale rather good in special hospitals for cancer. In the past, the reverse was true, and should therapeutic advances be long deferred, this atmosphere of despair may again return. Great as are the advantages of special services or hospitals for providing expert teams to care for such disorders as cancer or heart disease, it must be conceded that being with a group of patients, few of whom re-

cover and many of whom are known to die, is demoralizing to many of those who identify themselves quickly with fellow patients in more advanced stages of disease. It may well be that the best person to look after the inoperable cancer patient who has had definitive roentgen or chemotherapy is the family physician, and the best place for him to live and to die is at home. To direct a patient to a "cancer hospital" is in many cases equivalent to his hearing the death sentence. With the diagnosis of cancer or leukemia, which the patient may hear from others if the physician withholds it, hope must be provided, the fears based on lay reports must be allayed, and, with the diagnosis or direction to a special clinic, a new understanding must be conveyed to patient and family.

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## Section 3—Fluid and Electrolyte Balance

# 28

## Changes in Fluid Balance

C. A. Moyer and T. R. Harrison

### Introduction

Fundamental Variations in Fluid Balance

### General Principles

Clinical Recognition of Disordered Fluid Balance

Variation in Volume of Body Fluids

Distributional Shifts of Extracellular Fluid

Variations in Effective Osmolar Concentration of Body Fluids

Importance of Environmental and Incidental Factors

Summary of Bedside Recognition and Management of Commoner Disturbances of Fluid Balance

### INTRODUCTION

Water constitutes about 75 per cent of the body.<sup>1</sup> From a functional standpoint the water may be considered as being divided into compartments, the *intracellular water* comprising about 50 to 55 per cent of the body weight, and the *extracellular water* comprising about 20 to 25 per cent of the body weight. The extracellular water may be subdivided into the *intravascular extracellular component* (the water of the blood plasma and lymph), comprising about 5 per cent of the body weight, and the *extravascular extracellular component* (the water of the *interstitial fluid*), comprising about 15 to 20 per cent of the body weight.

In the chapter dealing with circulatory failure, alterations in the intravascular extracellular component have been considered in so far as this component is related to change in blood volume. In the following discussion no distinction need be drawn between the intravascular and extravascular components of the extracellular water, for they tend to vary together. However, a sharp distinction must be drawn between the extracellular water and the intracellular water, for they may vary independently.

<sup>1</sup> Recent measurements, using the dilution of deuterium oxide and of antipyrine as indices of body water, suggest that the amount of water available as solvent is much less than this, and may be as low as 50 to 60 per cent in healthy subjects.

### FUNDAMENTAL VARIATIONS IN FLUID BALANCE

The alterations which occur in the fluids of the body may be conveniently divided into three general categories:

**1. Variations in Volume.** It is obvious that since the predominant component of the body is water, changes in volume of the extracellular or intracellular fluid are necessarily directly correlated with alterations in the amount of water in these compartments.

**2. Variations in Effective Osmotic Concentration.** In the body, certain substances such as urea pass freely between the blood, the extracellular, and intracellular compartments. Such substances exert no differential osmotic effect because of their equal concentration. However, some substances, such as sodium, do not pass readily through the cell membranes, and hence exert a *differential or effective osmotic pressure* in the tissues in a manner analogous to the effective osmotic pressure exerted in the blood by plasma proteins.

Quantitatively, the various salts of sodium and potassium represent the chief solutes of the extracellular and intracellular fluids, respectively. Since chloride and bicarbonate—the most important extracellular anions—tend to vary reciprocally, a considerable alteration in either may occur without producing a significant over-all osmolar change. Potassium and phosphate are especially important in the intracellular fluid, about which relatively little is known. Since the discussion to follow will center mainly on the extracellular fluid, and since the chief factor which determines its effective osmotic concentration is its sodium content, the conditions to be discussed in relation to the variations in osmotic concentration will be those in which the sodium concentration of the extracellular fluid is altered. It

should be remembered, however, that such alterations tend to be minimized by the simultaneous retention or excretion of water, and that large changes in the total amount of sodium in the body may be reflected by little or no change in its concentration.

**3. Variations in Composition.** In this category there may be placed all alterations in the body fluids other than those which primarily affect water or sodium. The more important of these changes will be considered in the next chapter.

Since the fundamental function of the body fluids is the maintenance of constancy (or, more precisely, the limitation of variation) of the internal environment, it is of importance to realize that certain qualities are guarded more jealously than others. Under conditions of stress the healthy body will sacrifice volume, within certain limits, in order to maintain composition; and will sacrifice composition in order to maintain effective osmolar concentration.

### GENERAL PRINCIPLES

In considering the disturbances of fluid balance, certain general principles should be borne in mind:

1. Although water and sodium are interdependent and tend to vary together, the interdependence is not absolute, and deficit or excess of either in relation to the other occurs frequently.

2. Although variations in the total amount of extracellular fluid in the body are important, variations in the concentration of the various components of the fluid in relation to each other are often even more important (e.g., changes in content of sodium, chloride, bicarbonate, etc.).

3. Since the acid-base condition of the body is correlated with the content and distribution of sodium, which is closely related to the distribution of water, changes in fluid balance are intimately related to changes in acid-base balance. (This matter will be discussed in more detail in the next chapter.)

4. Primary disturbances in the volume and composition of the extracellular fluid compartment usually lead to secondary disturbances in intracellular volume and composition. Correction of the primary disorder with sodium chloride solution may prove ineffective unless the secondary disturbances in intracellular base are also cor-

rected. This may require the administration of fluids containing potassium, calcium, and magnesium.

5. *Under ordinary conditions the insensible (i.e., evaporative) loss of water (not saline solution) from the body, by means of the skin and respiratory tract, is about 1000 ml. per day.* This insensible loss is independent of sweating, and consists of the loss of water without loss of sodium or other salts. Therefore, the balance between fluid intake and urinary flow must be adjusted in such a way as to allow for this much free water, if serious disturbances of the fluid balance are to be prevented. In all instances except one (water intoxication), parenteral fluids should be hypotonic with respect to mineral content, the desired tonicity for intravenous or subcutaneous infusion being achieved with glucose.

6. *In addition to primary renal and cardiac disease, impairment in renal function sufficient to decrease the capacity of the kidney to preserve the normal volume and composition of the body fluids may occur in a wide variety of conditions (Chapter 19).*

7. *As a general rule, it may be stated that disturbances in the volume of extracellular fluid tend especially to produce manifestations in the circulatory system, while disturbances in the volume of intracellular fluid tend to produce manifestations in both the central nervous system and the neuromuscular apparatus.*

Changes in the fluid equilibrium may be spontaneous as the result of disease, or induced by improper therapy. The former disorders are of special importance in children, while the induced disorders are particularly common in the post-operative state and in renal disease. Both the spontaneous and the induced disturbances are encountered frequently in aged, infirm, or psychotic patients, and in persons acutely ill from almost any cause. Subjects who, because of coma or vomiting, require parenteral fluids are already suffering from a disturbance of fluid equilibrium, and the condition may be aggravated rather than benefited unless the type and volume of the administered fluid be selected with a clear comprehension of the nature of the disturbance.

In the interpretation of the disequilibrium the usual tendency to rely solely on laboratory procedures such as measurements of the volume of packed red cells, the plasma proteins, the

## CLINICAL MANIFESTATIONS INDUCED BY ALTERATIONS IN THE VOLUME OF BODY FLUIDS

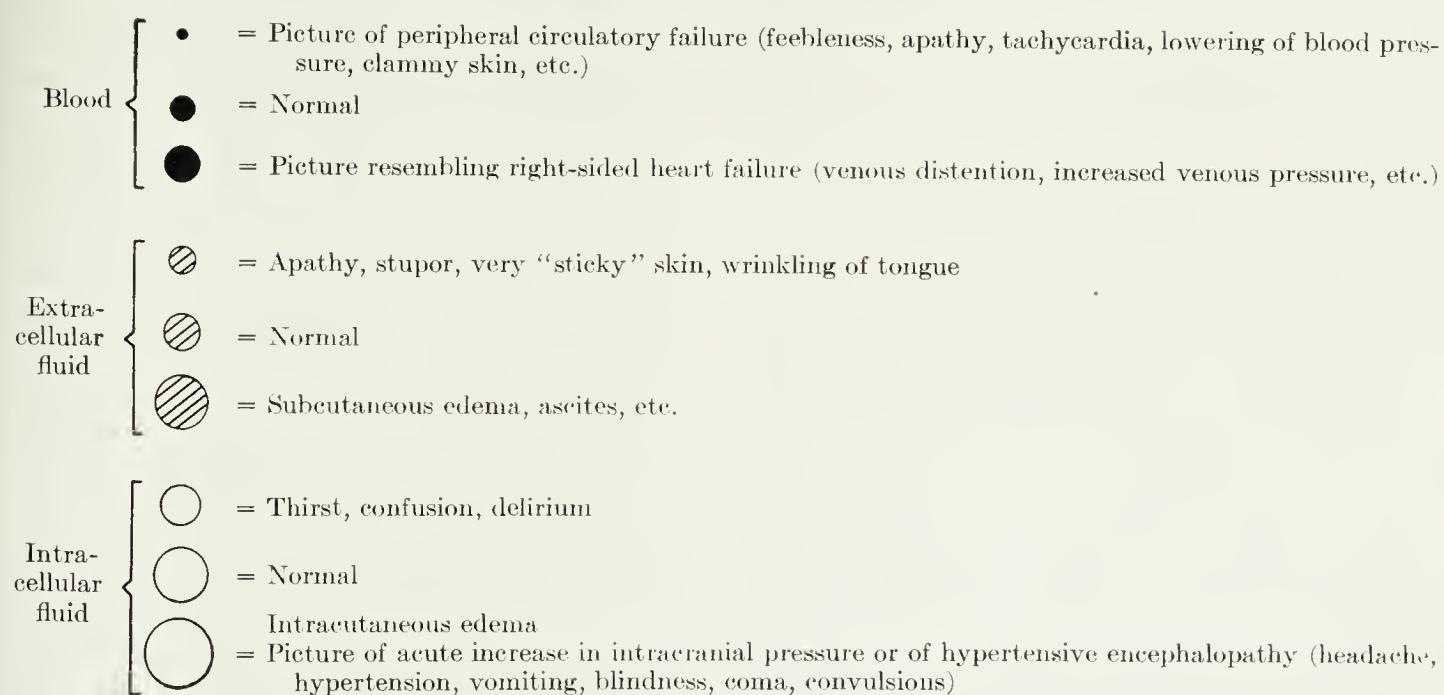


FIG. 32

chlorides, etc., is likely to lead to unsatisfactory results. Such measurements yield essential information in regard to compositional changes, but may be normal in the presence of serious disturbances of volume or osmolar concentration.

As a result of the studies of the past few years, it has become possible to achieve a clearer understanding of the clinical manifestations induced by the various disorders. *In many instances the clinical picture is a better guide to the underlying mechanism than the usual quantitative chemical measurements.* In most instances the important clue to significant intracellular base deficit is obtained from a history of long-continued inadequate food intake, or excessive loss of fluid through the extrarenal channels. This is particularly likely to occur in debilitated patients following surgical procedures. Therefore, a knowledge of the symptoms and signs produced by the commoner varieties of fluid disequilibrium is of great importance in the care of patients (fig. 32).

#### CLINICAL RECOGNITION OF DISORDERED FLUID BALANCE

**Specific Manifestations.** Certain phenomena are of especial importance because their presence is almost pathognomonic of disordered fluid balance. One of the most important of these is *information concerning the type and amount of oral and parenteral fluid which has been received.*

Such information will usually be obtainable from relatives, nurses, or physicians, rather than from the patient himself. Likewise, information should be obtained concerning *the amount of fluid lost by other channels*, realizing that such loss may be either the cause or the result of the disturbance. Thus, vomiting and diarrhea may produce extracellular fluid deficit, while excessive sweating (when associated with the drinking of abundant water) may lead to decreased osmolar concentration of extracellular fluid. On the other hand, sweating is a common result of acute hemorrhage, while vomiting, diarrhea, lacrimation, and salivation may be compensatory effects of water excess which commonly affect both the extracellular and (more particularly) the intracellular compartments.

*Thirst is the only specific complaint of disturbed fluid balance,* and points toward uncompensated water deficit, with increased osmolar concentration. Other symptoms, such as lassitude and syncope, which are frequently present, are common in other disturbances.

Of the specific objective findings, those observed in the skin and tongue are important. *Pitting subcutaneous edema* indicates extracellular fluid excess (at least locally), while *intracutaneous edema*, as shown by persistence of the observer's fingerprint in the skin after the firm pressure by the finger against a bony eminence, indicates intracellular fluid excess. "*Clamminess*" of the

skin (i.e., the cold and moist feeling of a dead fish) is suggestive of acute deficit of intravascular extracellular fluid, while "stickiness" of the skin (i.e., loss of elasticity with a lack of quick rebound when the skin is pulled into folds) points toward a more prolonged state of extracellular fluid deficit, involving both the extravascular and the intravascular components. *Dryness of the tongue and mucous membranes* suggests water deficit with increased osmolar concentration, while *longitudinal wrinkling of the tongue (shrinkage)* indicates extracellular deficit without osmolar change. These two signs may appear independently or together.

The presence of the *signs of peripheral circulatory failure* (as discussed in Chapter 14) is very suggestive of severe extracellular fluid deficit. This may be either of the primary intravascular type (e.g., hemorrhage) or of the primary extravascular type (e.g., vomiting). Such a state is accompanied by a *putty-like consistency of the muscles, and softness of the eyeballs*.

Of the specific evidence to be obtained by laboratory procedures, the significance of *hemodilution* and *hemoconcentration*, and of a low urinary pH and an *elevated urinary specific gravity* (when not due to glycosuria) is obvious. Alterations in osmolar concentration of extracellular fluid are detected best by *measurements of serum sodium concentration*, or total base concentration. When such measurements are not available, the sodium can be estimated with fair accuracy from the *sum of chloride and bicarbonate*, provided acetonuria is absent and renal function is not seriously impaired.

**Nonspecific Manifestations.** These, while not pathognomonic and while frequently the result of other causes, are of the greatest practical importance in indicating the type and severity of the disorder, provided one is certain, on the basis of the specific manifestations which have been mentioned, that a disturbance of fluid balance exists.

The various nonspecific symptoms which suggest extracellular fluid deficit are *lassitude, apathy, and loss of desire for food, water, and tobacco*. *Headache and visual disturbances* are, on the other hand, suggestive of water excess, involving particularly the intracellular compartment.

Among the valuable but nonspecific objective signs, those involving the nervous system are of

first importance. *Somnolence, stupor, and coma* may occur in the advanced stages of most of the disturbances of fluid balance but are especially suggestive of extracellular deficit, while *disorientation and mania* point toward acute water deficit, involving all compartments, and accompanied by increased osmolar concentration. The *signs of increased intracranial pressure* are encountered in persons with water intoxication and consequent intracellular fluid excess and diminished osmolar concentration, and include *twitchings and convulsions*. On the other hand, when there is relative water excess with diminished osmolar concentration, involving particularly the extracellular compartment, *muscular cramps* during or following exercise are likely to occur.

*Body temperature regulation* tends to be impaired with disturbances of fluid balance. Pronounced extracellular deficit reduces the effectiveness of thermostasis, and tends to raise or lower the temperature according to whether the environmental temperature is high or low.

The circulatory system displays various types of alteration. *Hypertension* and *bradycardia* commonly accompany increased intracranial pressure resulting from water excess, while *hypotension* and *pronounced tachycardia* characterize the state of advanced extracellular fluid deficit.

*Sunken eyeballs* suggest extracellular fluid deficit (usually associated with intracellular deficit also), unless there is coexistent wasting disease.

*Lowering of the specific gravity of the urine* is suggestive of water excess, provided the renal homeostatic function is not impaired.

## VARIATION IN VOLUME OF BODY FLUIDS

Since excess, deficit, or normality of volume may occur with either extracellular or intracellular fluid, there are nine theoretically possible volume alterations. However, since some of these states are much more common than others, they will be discussed in relation to their frequency and importance, rather than in relation to their logical order as outlined above.

**1. Deficit of Both Extracellular and Intracellular Fluid.** This is perhaps the most common and important of the disorders of fluid balance. The clinical picture varies according to the rapidity with which the deficit develops, and

hence this state may be subdivided into two overlapping states, one acute, the other chronic.

**ACUTE DEFICIT OF BOTH EXTRACELLULAR AND INTRACELLULAR FLUID (ACUTE UNCOMPENSATED WATER DEFICIT).** This condition is observed in subjects who for any reason abstain entirely from drinking water. Even though compensatory oliguria ensues, the evaporative loss of water (without solutes) by way of the skin and respiratory tract proceeds at its usual rate of about 1000 ml. of water per day. The body solutes tend to become concentrated, and a characteristic clinical picture develops.

The outstanding subjective phenomenon is intense thirst. Objectively, the tongue and mucous membranes are dry, but since there is relatively little volume deficit of extracellular fluid, the circulatory functions remain unimpaired. The urine volume declines and the specific gravity rises (unless there be coexisting advanced renal disease). As the condition becomes more severe the sensorium becomes clouded, disorientation appears, and maniacal behavior may develop, with coma finally supervening. Since abstinence from water drinking is rare, except in stuporous patients, a vicious cycle may ensue, the final coma resulting not so much from the original disorder causing the initial stupor, but rather from the results of the water deficit induced by the initial stupor. Aside from all of the conditions which lead to stupor, the chief circumstances under which acute water deficit occurs are of geographic origin (sea and desert).

The proper treatment of acute water deficit is the administration of water either orally or, when coma or some other contraindication exists, intravenously as glucose solution. Salt solution should not be given to such subjects at the outset, for their symptoms are mainly the result of the excessive sodium concentration which already exists. The amount of water needed is that which is sufficient to produce an adequate urine volume with a decline in the urinary specific gravity.

**CHRONIC DEFICIT OF BOTH EXTRACELLULAR AND INTRACELLULAR FLUID (CHRONIC COMPENSATED WATER DEFICIT).** This state is commonly observed in individuals who, over a considerable period of time, drink less water than an amount equal to the urine volume, plus the evaporative water loss. It is particularly common in psy-

chotic patients, in the aged, and especially when any acute—even relatively minor—disease sets in, and in patients who, because of organic disease of the brain, drugs, or severe pain, restrict water intake. Because the condition develops slowly, the kidney tends to compensate by excreting a urine relatively rich in sodium and other solutes. Except when the condition is very far advanced, or suddenly aggravated by an acute cessation of water drinking, there is, therefore, ordinarily little or no excess of sodium concentration, because the kidney tends to convert the condition of water deficit into a state of combined sodium and water deficit. The exact clinical state produced depends on the degree to which such compensation takes place.

In persons suffering from chronic deficit of both extracellular and intracellular fluid, the most striking initial features are lassitude, apathy, and diminished physical and mental vigor, associated with slow response to questioning. Because of the depression of the nervous system, thirst may be entirely absent. Desire for food and for tobacco are likewise impaired. The state of apathy may gradually give way to one of sleepiness or "dopiness," the patient's condition resembling that of an individual receiving large quantities of sedative drugs. If the condition is more severe, stupor and finally coma set in.

Other important manifestations which may be observed in such patients include "stickiness" of the skin, a putty-like consistency of the muscles, softness of the eyeballs, wrinkling of the tongue which is not necessarily accompanied by dryness, and some of the cardiovascular manifestations of shock, including lowering of the systolic blood pressure—and later of the diastolic—rapidity and feebleness of the pulse, etc. However, it is noteworthy that in such patients the skin usually does not have the cold, clammy, and ashen qualities ordinarily observed in subjects with other types of acute peripheral circulatory failure (Chapter 14).

The body temperature tends to be low in patients with chronic deficit of sodium and water, but may be increased if there is a proportionately greater water deficit, or when the condition occurs in the presence of high environmental temperature. As a rule, when the environmental temperature is below 85° F., the presence of an elevated body temperature in a patient suffering

from "dehydration" should make one think first of an acute severe primary deficit of free water rather than of sodium, or of some coexistent disease as the cause of the fever.

It should be emphasized that diminished elasticity of the skin, softening of the eyeballs, and longitudinal wrinkling of the tongue are not encountered in patients with acute water deficit alone. These signs, on the other hand, constitute strong evidence for the presence of combined sodium and water (i.e., extracellular) deficit. The latter condition is commonly associated with evidence of peripheral circulatory failure, whereas such evidence is usually absent in the case of deficit of free water, until it has become very severe.

It should be emphasized further that predominant deficit of extracellular fluid tends to cause quantitative changes (i.e., apathy, lassitude, sleepiness, stupor) in the mental processes, which are affected in velocity rather than in accuracy, while predominant deficit of intracellular fluid tends to cause qualitative changes in the mental processes (confusion, belligerency, disorientation, and delirium), the accuracy rather than the velocity being impaired.

In the treatment of extracellular fluid deficit, the following principles should be borne in mind: (1) The sole use of 0.9 per cent sodium chloride may lead to a state of acidosis as the result of dilution of the bicarbonate of the body. (2) The use of a combination of sodium chloride and sodium lactate (Hartman's solution) will tend to overcome this difficulty, but depends for its value upon the capacity of the liver to utilize the lactate and free the sodium for bicarbonate. If the liver is impaired as the result of preexisting disease, or a prolonged state of fluid deficit, this function may not proceed in normal fashion. (3) Recent work indicates that states of deficient extracellular fluid are often accompanied by the loss of potassium from the cells, and that this deficiency may produce important symptoms. (4) In the management of patients with extracellular fluid deficit, due consideration should be given to the state of acid-base balance. (5) At the present time it appears that the most generally useful solution is one which contains the lactates and chlorides of sodium and potassium. (6) The therapy of conditions characterized by extracellular fluid deficiency must be

modified according to whether a relative excess of free water or a relative lack of it coexists.

**2. Extracellular Fluid Excess and Intracellular Fluid Excess.** This is "water intoxication" and the state can be induced in experimental animals by administering water at a rate faster than the kidneys can excrete it. Under such circumstances the additional water is distributed in both the extracellular and the intracellular compartments.

As has been mentioned, the normal kidney possesses a remarkable power of adjustment as regards water and sodium, any excess of either the one or the other being compensated for within a few hours by changes in the composition of the urine. However, in the case of water, as in that of sodium, the kidney which is acutely damaged either primarily (acute nephritis, eclampsia), or secondarily as the result of peripheral circulatory failure or of unknown mechanisms, may exhibit a deficient regulatory power. In the normal subject the clinical picture of water excess does not occur until after very large amounts of water are ingested. However, in the case of certain patients, the regulatory power of the kidney is so impaired that the drinking of water in only slightly excessive quantities, or the administration of sodium-free fluids, such as 5 per cent glucose, may induce the state of "water intoxication."

The chief manifestations are related to: (1) increased intracranial pressure (including headache, visual disturbances, papilledema, vomiting, muscular twitchings, bradycardia, coma, stertorous breathing, and convulsions), and (2) excretion of water via extrarenal channels (including vomiting, diarrhea, lacrimation, and salivation). Acute hypertension exists in many instances. Edema of the skin rather than the subcutaneous tissues may occur, and can be demonstrated by observing that one's fingerprints are reproduced in the patient's skin following pressure against a bony surface such as the tibia. In other patients both intracutaneous and subcutaneous edema may occur. Unless there is coexistent renal impairment, the urine displays a low gravity and very low chloride content; the blood displays evidence of dilution of solutes and red corpuscles.

The exact mechanism whereby the kidney, which may display no evidence of any pathologic lesion, loses its water-regulating power has not been elucidated fully, although there is

some evidence that increased activity of the posterior lobe of the pituitary may sometimes be concerned, and the consequent excessive anti-diuretic action of this gland may be responsible for water retention. When kidney disease of certain types such as that seen in eclampsia and in acute glomerular nephritis exists, symptoms of water intoxication may occur even though the water intake be normal. The exact relationship between hypertensive encephalopathy, cerebral edema, and water intoxication remains to be elucidated, but there can be little doubt that under certain circumstances such a relationship exists, and that the acute type of hypertensive encephalopathy so often seen in subjects with eclampsia or acute glomerular nephritis is related not only to vascular alterations, but also to water excess in the body.

The symptoms of excessive hydration are dependent upon the increased volume of water and the relative excess of water as compared to sodium. When the clinical manifestations of water intoxication permit, restoration of normal fluid volume and sodium concentration may be accomplished by simply withholding all fluids, utilizing the water consumed by normal metabolic processes (respiration, evaporation, and urine output) as a means of accomplishing the necessary dehydration. When the clinical symptoms are so acute as to endanger life, it may be necessary to administer concentrated human serum albumin and/or hypertonic solutions of sodium salts. The administration of these solutions is attended by a real danger of inducing pulmonary edema. The possibility of such a complication more than justifies conservative treatment in most instances.

**3. Extracellular Fluid Excess with Normal Volume of Intracellular Fluid.** This is the situation which prevails in most patients with chronic edema. As already pointed out, the local tissue factors vary according to the type of edema, but the renal factor is present in all types of generalized edema, and appears to consist of primary sodium retention and secondary water retention. For further discussion of this type of disturbance in fluid balance the reader is referred to Chapter 20.

**4. Extracellular Fluid Excess with Intracellular Fluid Deficit.** In this condition the clinical manifestations are, in the main, the result of the deficit of intracellular fluid, the excess of

extracellular fluid causing no manifestations other than pitting edema, if it is sufficiently marked.

This condition may be observed in certain edematous patients with congestive heart failure who are treated by deprivation of water. However, in such patients there is likely to be a deficit of extracellular as well as intracellular fluid in the upper part of the body, and hence this state will be discussed later.

This type of disturbance is commonly seen postoperatively, when an individual with impairment of the renal capacity to concentrate sodium (such an impairment exists in most subjects for two or more days following an operation) is given 0.9 per cent sodium chloride as the sole source of fluid. In such an instance the insensible water loss, unless balanced by a correspondingly high level of urinary sodium excretion, leads to the symptoms of intracellular fluid (water) deficit, as already mentioned, even though the actual amount of water in the body is greater than normal. This condition may, in large measure, be avoided by postoperative administration of 0.6 per cent (rather than 0.9 per cent) sodium chloride solution, isotonicity being achieved with glucose. The larger volume of water relative to sodium allows for insensible loss without an attending concentration of solutes in the urine.

Aside from the presence of edema of the subcutaneous tissues, the clinical manifestations of this state resemble those of intracellular fluid deficit in general.

**5. Extracellular Fluid Deficit with Intracellular Fluid Excess.** This state may be induced in animals or man under conditions which promote the excretion of sodium and the retention of water. It is produced readily by the excessive administration of glucose, subcutaneously or intraperitoneally. Under such circumstances the glucose may be absorbed slowly, while sodium diffuses rapidly into the injected fluid from the extracellular compartment, and the water left behind diffuses into the cells from the extracellular fluid. The manifestations of this state resemble those of excess of intracellular fluid, in general (acute increase in intracranial pressure—"water intoxication"), and, in addition, the manifestations of acute peripheral circulatory failure tend to develop if the extracellular fluid deficit becomes sufficiently severe.

**6. Extracellular Fluid Deficit with Normal Volume of Intracellular Fluid.** Since any pronounced deficit of extracellular fluid tends to be partially restored at the expense of the intracellular fluid, this state can exist either when sodium loss is greater than water loss, or for a short time under conditions in which there is very rapid loss of extracellular fluid. Such circumstances may occur during the acute crises of Addison's disease, and may also prevail in persons with Asiatic cholera, and in infants during some of the other acute diarrheal states. The clinical picture is essentially that of acute peripheral circulatory failure attended by hemoconcentration, these manifestations resulting from the acute decline in blood volume rather than from the decline in the extravascular extracellular fluid. After a time the typical manifestations of extravascular extracellular fluid deficit develop, and the patient displays "sticky skin," "putty muscles," wrinkling of the tongue, and apathy or stupor.

The outstanding clinical manifestations of the various disturbances of the volume of the body fluids are summarized in figure 32.

#### DISTRIBUTIONAL SHIFTS OF EXTRACELLULAR FLUID

Aside from those conditions which have been considered, there are states in which the total volume of fluid in the extracellular and intracellular compartments may be essentially normal, but in which the distribution of such fluid between the various parts of the body may be seriously abnormal.

Perhaps the most striking example of this state is seen in those patients with severe congestive heart-failure, who are kept on a markedly reduced water intake for a considerable period. Such individuals often have well-marked edema of the lower extremities, while the upper part of the body displays evidence of extracellular fluid deficit (wrinkling of the tongue, loss of elasticity of the skin, etc.).

Another common cause of distributional shifts in the extracellular fluid is trauma. Extracellular fluid and blood (cells and plasma) move rapidly into injured areas and tend to remain there for several days. Similar states occur following extensive injury to the skin, either chemical or thermal, and in certain acute infectious diseases which are characterized by widespread capillary

damage (e.g., Rocky Mountain spotted fever). Regardless of the cause, the movement of fluid to the diseased part tends to result in deficit of extracellular fluid in the remainder of the body. In correcting this by the administration of fluid and of blood, one should remember that after a few days there may be a tendency for the accumulations in the injured areas to move back into the body as a whole, and that too vigorous therapy at that time may result in a state of extracellular fluid excess.

#### VARIATIONS IN EFFECTIVE OSMOLAR CONCENTRATION OF BODY FLUIDS

From the foregoing discussion it will be clear that variations in water and in sodium tend to proceed together, and the regulatory activity of the kidneys tends to alter volume of body fluids when this is necessary in order to maintain a constant sodium concentration. It is, therefore, not surprising that alterations in osmolar concentration (i.e., in sodium concentration) occur less commonly than alterations in volume, and are likely to be encountered only either when the kidneys are impaired or when changes occur at a rate too rapid to permit these organs to make the necessary compensatory adjustments.

**1. Excessive Osmolar Concentration.** The most outspoken, but fortunately rare, state is that which occurs when a sodium-rich fluid such as sea water is ingested. Thirst is intensified rather than relieved.

The commoner but less sudden causes of excessive osmolar concentration are acute water deficit, which has been discussed, and the continued administration of 0.9 per cent sodium chloride as the sole source of fluid to patients with disturbed renal function. The insensible water loss tends, under such circumstances, to lead to an increase in sodium concentration in the extracellular fluid, and if this condition cannot, as is frequently the case, be compensated for by the excretion of a urine sufficiently rich in sodium, water is drawn from the intracellular compartment with consequent intracellular fluid deficit. This state has already been discussed.

**2. Diminished Osmolar Concentration.** A common cause of this condition is excessive sweating, with a corresponding rapid loss of sodium chloride *when it is accompanied by copious ingestion of water*. The resulting decline in osmolar concen-

tration leads to cramps in the muscles ("miner's cramps," "heat cramps") which are quickly alleviated by the ingestion of salt, and are prevented by the use of diluted sodium chloride solution for drinking purposes.

Any other condition in which there is rapid loss of extracellular fluid or blood from the body associated with profuse drinking of water, may lead to a similar state. When the condition is outspoken the symptoms are those already discussed as water intoxication (excess of both extracellular and intracellular fluid).

In these and other states of altered osmolar concentration, the clinical pictures tend to be a combination of those which have been described in relation to the various volume alterations, and those which accompany the compositional changes to be considered in the next chapter.

### IMPORTANCE OF ENVIRONMENTAL AND INCIDENTAL FACTORS

One of the important practical points in regard to fluid balance is the following: *The type of disturbance is conditioned not only by the nature of the underlying disease process, but also by various associated factors such as the acuteness of onset, the amount of water ingested, the environmental temperature, etc.* Diabetic coma may be selected as an example of this principle. Here, as in other acidotic states, when the initial compensatory processes (increased elimination of carbon dioxide, excretion of an acid urine, formation of ammonia by the kidneys) fail to overcome the acidosis, a rapid renal excretion of organic sodium salts (and of water) takes place as a final means of disposal of acidic ions. Thus extracellular fluid deficit is an almost universal feature of diabetic coma. When this state develops rapidly, there may be little change in intracellular fluid volume, but when, as is usually the case, it sets in over a period of several days, shifts of water (and potassium) from the cells take place, and the picture is then that of combined extracellular and intracellular volume deficit. If, however, the patient happens to drink a large amount of water during the development of diabetic acidosis, the final state may be one of extracellular deficit with intracellular excess (water intoxication), and a similar state may be induced by the use of large amounts of water, as glucose solution, in treating such subjects. The patients with diabetic coma may have

a diminished, normal, or elevated temperature, depending on the environmental temperature and the presence of complications.

Another example of the same general principle is acute diarrhea occurring in infancy. When the loss of fluid develops with great rapidity and severity, there occurs initially a state in which the deficit is largely confined to the extracellular compartment, both intravascular and extravascular. At a later stage there is a tendency toward increased osmolar concentration of the extracellular fluid, because the water which is being lost insensibly is not replaced in normal fashion. This leads to intracellular water loss. The picture may be altered further by compositional changes incident to chloride loss in vomitus, base loss in stools, ketosis resulting from starvation, and retention of acid metabolites consequent to depressed renal function. It is, therefore, not to be expected that any single clinical picture in relation to fluid balance will be encountered in all instances of acute diarrhea.

In treating infantile diarrhea and other disorders of fluid balance which occur in young patients, one important point should be borne in mind. The rate of insensible fluid loss, though actually less, is relatively greater in such patients than in adults, being about 1.3 ml. per kg. per hour in infants, and about 0.8 ml. per kg. per hour in older children.

### SUMMARY OF BEDSIDE RECOGNITION AND MANAGEMENT OF COMMONER DISTURBANCES OF FLUID BALANCE

- I. Deficiency of extracellular and intracellular fluid:
  - A. *Acute water deficit.* The outstanding early feature is thirst, followed later by weakness, fast pulse, and disorientation. The condition may be prevented by giving sufficient water (usually about 1500 ml. daily, except in summer when larger amounts are necessary) to compensate for evaporative loss, and should be treated by the oral administration of water or the intravenous administration of glucose in water, in amounts sufficient to produce lowering of the specific gravity of the urine and to relieve thirst.
  - B. *Chronic water deficit.* The outstanding features are a story of small water intake

(as the result of stupor or drugs), loss of elasticity of the skin, wrinkling of the tongue, and eventual peripheral circulatory failure. The treatment consists of the use of hypotonic salt solution containing potassium as well as sodium, and, later, the daily administration of water, as indicated above.

- II. Excess of both intracellular and extracellular fluid, or *water excess*. This condition usually occurs when a person with renal functional impairment (often without structural renal disease) is given more water than is excreted by the evaporative and renal routes. The outstanding features are those of increased intracranial pressure often associated with rise in blood pressure, plus excretion of water via the gastrointestinal tract. Whenever possible, the signs and symptoms of water intoxication are treated best by withdrawal of all fluids, thereby permitting the water required for metabolic needs to assist in dehydrating the patient. Occasionally the symptoms may be so severe as to require the intravenous administration of concentrated human serum albumin (5 to 10 Gm./hr. for two to three hours), or solutions of concentrated sodium salts (100 to 300 ml. of 3 per cent sodium chloride and  $\frac{1}{3}$  normal sodium lactate). Either of these solutions may induce pulmonary edema, and may require venesection and rapid digitalization.
- III. Excess of extracellular fluid only. This is edema and requires no comment.
- IV. Distributional shifts of extracellular fluid. This is the state which occurs when there is edema of the dependent portion of the body, plus signs of fluid deficit (i.e., thirst, sticky skin, wrinkling of the tongue) in the remainder of the body. The management is that of the cause of the edema, plus the administration of sufficient water to relieve thirst, and of salt solutions and plasma to correct the signs of extracellular fluid deficit.

At the risk of tiresome reiteration, the following principles concerning therapy are again emphasized:

1. The choice of the solution to be used and

the decision as to the volume to be administered depend upon the clinical picture.

2. A patient who is thirsty generally needs water and, unless he can retain it by mouth, should receive glucose solution until thirst is relieved.

3. When peripheral circulatory failure exists, whole blood is generally preferable to plasma, unless there is evidence of hemoconcentration.

4. When the signs of extracellular fluid deficit have developed acutely, 0.9 per cent sodium chloride solution or, preferably, "balanced" salt solutions containing the chlorides and lactates of sodium and potassium, should be given until these signs have disappeared, with due regard for the possibility of cardiac failure and pulmonary edema.

5. When the signs of extracellular fluid lack have developed gradually, there will usually be coincident evidence of intracellular fluid lack, and, under these conditions, there is deficiency of potassium as well as of sodium. The water deficit is generally proportionately greater than the sodium deficit. Hence isotonic glucose solution should be alternated with isotonic "balanced" salt solution, and potassium salts should be administered orally, if possible.

6. One can usually avoid inducing disorders of fluid balance in patients receiving fluids only parenterally, by the following procedure. Glucose (5 or 10 per cent) in water should be administered in an amount equal to the sum of insensible loss (about 1000 ml. daily, in an adult), plus the volume of the previous day's urine. In addition, hypotonic solution of sodium and potassium (table 29) should be administered in an amount equal to the estimated daily loss in the sweat or other secretions.

The most important symptoms of the common disorders characterized by deficit of body fluids, and certain general principles of treatment, are summarized again in table 28, while the composition of the most generally useful fluids for parenteral administration are indicated in table 29.

Throughout this chapter the importance of changes in water and in sodium has been stressed, as it is the total amount of these substances in the body and their relation to each other which is of primary importance in regard to fluid

Table 28

## CLINICAL MANIFESTATIONS OF SOME OF THE MORE IMPORTANT TYPES OF BODY FLUID DEFICIT

	<i>Condition</i>			
	<i>Extracellular Fluid Deficit; Intracellular Fluid Deficit</i>		<i>Extracellular Excess in One Part of the Body; Extracellular Fluid Deficit in the Rest</i>	<i>Extracellular Fluid Deficit; Intracellular Fluid Normal</i>
	<i>Acute Type</i>	<i>Chronic Type</i>		
Approximate synonym	Acute (uncompensated) water deficit	Chronic (compensated) water deficit	Distributional shift of extracellular fluid	Acute salt water deficit
Most important causes	Sudden cessation of taking in water	Prolonged intake of water that is slightly less than the minimal rate of its loss	Trauma, rapid formation of peritoneal or pleural transudates or exudates, rapid formation of edema	Rapid vomiting, early stages of diarrhea, hydronephrotic atrophy with water diuresis
Skin	Dry; sweating diminished	Wrinkled and sticky	Dry and sticky in areas not injured	Dry and sticky
Tongue and mucous membranes	Dry and usually red	Dry and wrinkled	Wrinkled (may be moist if water is taken)	Wrinkled (may be moist if water is taken)
Nervous system	Disorientation, mania, coma	Weakness, apathy, somnolence	Weakness, somnolence, stupor	Weakness, somnolence, stupor
Circulatory system	Fast pulse, peripheral failure (late)	Fast pulse, peripheral failure (late)	Fast pulse, peripheral failure	Fast pulse, peripheral failure
Others	Elevated temperature, great thirst if consciousness is not too severely impaired	Temperature may be high or low, no thirst, no appetite	Temperature low or high, depending on environmental temperature	Temperature low or high, depending on environmental temperature
Urine	Oliguria, anuria, high specific gravity, high chlorides	Oliguria, high specific gravity, chloride may be high	Urine flow varies, depending on water intake and degree of peripheral circulatory failure	Urine flow varies, depending on water intake and degree of peripheral circulatory failure
Plasma	Increased concentration of Na and chloride and protein	Little change in concentration of anything	Electrolyte concentration normal or diminished if water is taken and retained	Electrolyte concentration normal or diminished if water is taken and retained
Blood	High hematocrit	Hematocrit normal or slightly elevated	Elevated hematocrit if rate of shift is rapid	Elevated hematocrit if rate of shift is rapid
Treatment	Glucose in water, intravenously; water orally or rectally	Slightly hypotonic balanced salt solutions containing potassium; blood	Balanced salt solutions; plasma; blood	Balanced salt solutions; plasma; blood

Table 29

## USEFUL TYPES OF REPLACEMENT FLUID

Deficiency	Replacement
Body Water	5% dextrose in water
Acute Blood Loss	Whole blood
Traumatic Loss of Plasma and Interstitial Fluid	Isotonic balanced salt solution and/or Plasma from a single donor in order to minimize the risk of serum hepatitis
Acute Extracellular Fluid Loss	Hypotonic balanced sodium chloride solution (Equivalent to 100 mEq. sodium per liter) Sodium chloride: 4.5 Gm. Sodium lactate: 2.5 Gm. 5% dextrose: 50 Gm. Made up to 1 liter
Chronic Extra- and Intracellular Fluid Loss	Hypotonic balanced sodium and potassium solution (equivalent to 100 mEq. sodium, 13 mEq. potassium, and 77 mEq. chloride per liter) Sodium chloride: 4.5 Gm. Sodium lactate: 2.5 Gm. Potassium chloride: 1.0 Gm. 5% dextrose: 50 Gm. Made up to 1 liter
Dehydration and Acidosis Diabetic coma at onset of treatment	Isotonic basic sodium solution (equivalent to 150 mEq. sodium per liter) Sodium bicarbonate: 13 Gm. or Sodium lactate: 19 Gm. Made up to 1 liter
Acute Potassium and Phosphate Deficiency For use following institution of replacement therapy in diabetic acidosis	Potassium phosphate mixture (equivalent to 28 mEq. potassium and 16 mEq. phosphorus per liter) $K_2HPO_4$ : 2.0 Gm. $KH_2PO_4$ : 0.4 Gm. 5% dextrose: 50 Gm. Made up to 1 liter
Vomiting and Alkalosis	Acid solutions Sodium chloride: 8.5 Gm./l Ammonium chloride: 20 Gm./l (2% sol.)

balance. Nevertheless, other significant compositional changes may occur in the body fluids and may induce important clinical manifestations. These will be considered in the chapter to follow.

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## Changes in Electrolyte Composition

M. F. Mason and T. R. Harrison

### Alterations in Acid-Base Balance

#### Concept of Buffers

- Quantitative Aspects of Buffer Systems of the Body
- Composition of Blood Plasma in Terms of Electrolytes
- Classification of Acid-Base Disturbances
- Clinical Manifestations of Acid-Base Disturbances

### Alterations in Chlorides

#### Excess of Chloride

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### Calcium and Phosphorus

#### State of Calcium in Body Fluids

#### Vitamin D in Relation to Calcium and Phosphorus

#### Parathyroid Gland in Relation to Calcium and Phosphorus

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#### The Kidney in Relation to Calcium and Phosphorus

#### Factors Affecting Plasma Level of Calcium and Phosphorus

#### Serum Alkaline Phosphatase

### Common Disorders of Bone in Relation to Calcium and Phosphorus

#### Deficiency of Bone Matrix (Osteoporosis)

#### Defective Deposition of Phosphorus and Calcium in Bones (Osteomalacia)

#### Increased Loss of Calcium and Phosphorus from Bones

### Certain Considerations of Nephrolithiasis

### Magnesium

In the preceding chapter, alterations in the volume and in the osmolar concentration of the body fluids were discussed. Since in the case of the extracellular fluid the chief determinant of osmolar concentration is sodium, alterations in the sodium ion in the body were likewise considered. The present chapter will be concerned with the mechanisms and manifestations of alterations in the other electrolytes. Since the types and causes of disordered electrolyte composition are numerous, only the most important will be discussed.

### ALTERATIONS IN ACID-BASE BALANCE

**Concept of Buffers.** The chemical processes of metabolism are of such a nature that large amounts of acid substances are produced. These acids constitute those which are intermediate products in the breakdown of foodstuffs, and those which are the final products in these processes. Despite such continuing production of acid, the body possesses efficient mechanisms for preventing any striking increase in the acidity of its fluids. The ultimate disposal of those acids which

are end products of metabolism involves the excretion of carbon dioxide by the lungs, and of organic and inorganic acids by the kidneys. Such excretory processes do not, however, proceed instantaneously, and, immediately after the formation of acid metabolites and during the processes of their transport, the buffering systems of body fluids and cellular structures play a fundamental role in protecting against marked increases in acidity in the internal environment.

The law of mass action states that in the case of any reversible chemical reaction the product of the active masses of the resultants of the reaction, raised to the power of their coefficients, divided by the product of the active masses of the initial reacting substances, raised to the power of their coefficients, is a constant at a given temperature. When applied to the particular case of a univalent, weak (i.e., slightly ionized) acid, in solution sufficiently dilute so that molar concentration is approximately equal to active mass, a simpler statement obtains; i.e., for a given temperature the ratio of the products of the concentrations of resultants and of reactants is constant.

Since the bicarbonate-carbonic acid system is one of the most important buffers in the body, carbonic acid may be used as an illustration.

This choice is not too fortunate in that, strictly speaking, carbonic acid in aqueous solution as ordinarily designated actually represents two entities—anhydrous  $\text{CO}_2$  and its hydration product,  $\text{H}_2\text{CO}_3$ . The system may be treated by the law of mass action in most instances as if all of the  $\text{CO}_2$  were present as a weak acid,  $\text{H}_2\text{CO}_3$ , in spite of the fact that the actual  $\text{H}_2\text{CO}_3$  is much smaller in amount and rather highly dissociated. In addition, certain kinetic features of the behavior of carbonic acid are quite different from those of other weak acids. With these reservations the equation of its ionization may be written:



Ignoring the reaction with water, this ionization is often written:



i.e.,  $\text{H}_3\text{O}^+$  is the conventional hydrogen ion designated in its more likely state as a hydrated proton or "hydronium" ion. Subsequently, in this text, the term "hydrogen ion" will be employed in designating this particle.

Applying the mass law, we may write:

$$\frac{[\text{H}_3\text{O}^+] \times [\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3] \times [\text{H}_2\text{O}]} = k,$$

in which the brackets designate the molar concentrations of the components concerned. Inasmuch as this function for water is not readily defined, the expression becomes

$$\frac{[\text{H}_3\text{O}^+] \times [\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} = k[\text{H}_2\text{O}] = K_a,$$

in which case  $K_a$  is the value of the equilibrium constant for carbonic acid at a given temperature.

It may be seen that, if the mass law obtains, the addition of bicarbonate ion (e.g., as the completely dissociated sodium bicarbonate) to this system containing the weakly dissociated carbonic acid will tend to cause reassociation of hydrogen and bicarbonate ions. In other words, the equilibrium will be shifted, with an increase in the amount of undissociated carbonic acid, and a decrease in the number of hydrogen ions. Thus that function of the hydrogen-ion concentration

defined as  $\text{pH} \left(= -\log [\text{H}_3\text{O}^+] = \log \frac{1}{[\text{H}_3\text{O}^+]}\right)$

is increased. This is an example of the "common ion effect," and is fundamental to the mechanism of all buffer action, for in the body the various buffer systems comprise a series of weak acids in the presence of their salts. The dissociation of these weak acids is kept depressed by the presence of the large excess of anions of the corresponding salts. When acids which are stronger (i.e., more highly dissociated) than those of the buffer systems are added, they react with anions of the buffer acids by donating their hydrogen ions (protons) to the anion of the buffer salt. The stronger acid is thereby converted into a salt anion at the expense of the production of more of the weak buffer acids resulting from this decomposition of the buffer salts. The dissociation of these weak acids, however, is kept relatively depressed as long as appreciable amounts of the

buffer salts remain (common ion effect!); i.e., only a slight increase in hydrogen-ion concentration occurs.

The buffer effect is found to be maximal; that is, the hydrogen-ion increase consequent to addition of a given amount of strong acid is minimal when the ratio of the molar concentrations of the weak acid and the salt of the weak acid in the system is unity. With deviations of this ratio from unity, the buffer effectiveness correspondingly declines. This phenomenon of buffer action is ordinarily expressed quantitatively in titration curves which may be determined experimentally, or calculated with the aid of the Henderson-Hasselbalch equation (see below).

The effectiveness of such buffer systems may be seen readily by comparing the change in pH produced when, for example, 10 ml. of 0.1 N HCl (a strong acid) is added to 90 ml. of each of the following: (1) water; (2) 0.1 N NaCl, and (3) a closed system containing a mixture 0.1 N, in respect to both carbonic acid and sodium bicarbonate. Thus the pH of the water and sodium chloride solutions declines from 7.0 to approximately 2. That of the carbonic acid-sodium bicarbonate solution changes from approximately pH 6.4 to 6.2.

**Quantitative Aspects of Buffer Systems of the Body.** The modern approach to the understanding of acid-base relationships within the body is based upon the proved validity of the Henderson-Hasselbalch equation, which defines the equilibrium in buffer systems. The meaning and significance of this expression may now be reviewed briefly.

The equation may be derived readily as follows: Application of the law of mass action to the dissociation of carbonic acid (see above) permits definition of the equilibrium constant as

$$\frac{[\text{H}_3\text{O}^+] \times [\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} = K_a (= 3.5 \times 10^{-7}, 18^\circ \text{C.}).$$

The addition of sodium bicarbonate to a solution of carbonic acid will provide a large excess of bicarbonate ions ( $\text{HCO}_3^-$ ) and, as previously explained, decrease the concentration of hydrogen ions. Since bicarbonate salts are completely dissociated, whereas carbonic acid may be considered as dissociated to only a very slight extent, in a mixture of carbonic acid and bicarbonate

salt the molar concentration of bicarbonate ions will be essentially equivalent to the molar concentration of the salt. Thus it may be assumed that only a negligible fraction of the bicarbonate ions arises from the dissociation of the carbonic acid, as this dissociation has been depressed by addition of the salt (common ion effect). The expression defining the equilibrium constant may, therefore, be modified as a close approximation to:

$$\frac{[\text{H}_3\text{O}^+] \times [\text{BHCO}_3]}{[\text{H}_2\text{CO}_3]} = K_a,$$

in which  $[\text{BHCO}_3]$  is the molar concentration of the sodium bicarbonate in the system. Simple algebraic rearrangement yields

$$[\text{H}_3\text{O}^+] = K_a \cdot \frac{[\text{H}_2\text{CO}_3]}{[\text{BHCO}_3]},$$

and it is seen at once that the hydrogen-ion concentration of such a system is readily calculable, providing the values of the equilibrium constant for carbonic acid and the molar concentrations or ratio of the acid and salt are known.

Since the actual molar concentration of hydrogen ions in the body fluids is extremely small—i.e., of the magnitude of  $10^{-7}$  or 0.0000001 M, it has been convenient to express such concentrations in terms of the reciprocals of their logarithms (= negative logarithms, in this case  $-\log_{10} [\text{H}_3\text{O}^+]$ ), that is, in terms of pH. The equation above, which defines the hydrogen-ion concentration of the buffer system carbonic acid–alkali bicarbonate, is converted to the pH notation by the expedient of taking its logarithm, and in this form it becomes

$$\text{pH} = \text{p}K_a + \log \frac{[\text{BHCO}_3]}{[\text{H}_2\text{CO}_3]},$$

in which  $\text{p}K_a$  is the negative logarithm of the equilibrium constant. Thus, inasmuch as  $-\log \text{H}_3\text{O}^+ = \text{pH}$ ,  $-\log K_a = \text{p}K_a$ .

In those circumstances in which molar concentration and “active” concentration are not equivalent (i.e., in other than very dilute solutions), the molar concentrations must be corrected to “active” concentrations by employment of the activity coefficient, a function which is either determined experimentally or, under certain circumstances, calculated from collateral data. This is usually necessary only in the case of the salt anion. Thus, if the activity coefficient is

designated as  $\gamma$ ,

$$\text{pH} = \text{p}K_a + \log \frac{[\text{BHCO}_3]\gamma}{[\text{H}_2\text{CO}_3]}.$$

For convenience, prior to conversion to pH notation this function may be incorporated into the value of the equilibrium constant as  $\frac{K_a}{\gamma} = K'_a$ , which then becomes  $\text{p}K'_a$ , and the equation, which is that of Henderson and Hasselbalch, becomes

$$\text{pH} = \text{p}K'_a + \log \frac{[\text{BHCO}_3]}{[\text{H}_2\text{CO}_3]},$$

or, expressed for buffer systems in general,

$$\text{pH} = \text{p}K'_a + \log \frac{[\text{salt}]}{[\text{acid}]}.$$

The value of  $\text{p}K'_a$  is a function of the strength of the weak acid of the buffer pair—that is, its degree of dissociation.  $\text{p}K'_a$  for carbonic acid in serum is 6.1. Since the molar ratio of bicarbonate and carbonic acid in serum is normally about 20 to 1, and since the log of 20 is 1.3,

$$\text{pH} = 6.1 + 1.3 = 7.4$$

Note that in such a calculation the actual concentrations need not be known if the value of the ratio is known, as only the *ratio* is calculated from the concentrations.

The same general principles obtain for the other buffer systems of the body, of which the following are some of the most important: protein (BP/HP), hemoglobin (BHb/HHb), and phosphate ( $\text{B}_2\text{HPO}_4/\text{BH}_2\text{PO}_4$ ). Each buffer acid of these systems has its characteristic dissociation constant, although in the case of proteins and the chromoprotein hemoglobin this is somewhat complicated by each protein having several dissociating groups and hence several equilibrium constants; i.e., the proteins are polyvalent ampholytes capable of either accepting or donating protons, thus behaving as either acids or bases. In the body these systems are in equilibrium with one another, so that we may write:

$$\begin{aligned} \text{pH} &= \text{p}K'_{a(1)} + \log \frac{[\text{salt}]}{[\text{acid}]} = \text{p}K'_{a(2)} \\ &\quad + \log \frac{[\text{salt}]}{[\text{acid}]} = \text{p}K'_{a(3)} + \log \frac{[\text{salt}]}{[\text{acid}]} \dots \text{etc.} \end{aligned}$$

in which the different buffer systems are indicated by the subscript to their  $\text{p}K'_a$ 's.

The point to be emphasized is that the state

of any one buffer system defines the equilibrium for all the others in the same system—e.g., in the plasma and interstitial fluid. These are in turn in equilibrium with the buffer systems in the erythrocytes and, in a less well-described manner, with those of the intracellular space.

Since it so happens that the total amount of CO<sub>2</sub> present as bicarbonate and carbonic acid is readily measured by gas analysis, and since, if the pH is directly determined, the molar concentrations or ratio of bicarbonate and carbonic acid are readily calculable with the Henderson-Hasselbalch equation, it is the bicarbonate system which is usually examined in order to ascertain the state of the buffers in the body, and hence the acid-base balance of the patient.

The peculiar feature of the bicarbonate-carbonic acid buffer system is that the increase in carbonic acid concentration occurring when the system buffers stronger acid is greatly minimized by the fact that most of the excess acid dehydrates (H<sub>2</sub>CO<sub>3</sub> ↔ CO<sub>2</sub> + H<sub>2</sub>O), and the liberated CO<sub>2</sub> is removed from the organism via the lungs. It follows that a large fraction of the bicarbonate ion in the system may be converted to carbonic acid, with only a slight corresponding alteration of the BHCO<sub>3</sub>/H<sub>2</sub>CO<sub>3</sub> ratio of arterial blood. Thus the bicarbonate system is a particularly effective buffer against stronger acids; on the other hand it is relatively ineffective when the invading acid is carbonic acid itself, as the salt/acid ratio is already considerably removed from unity (see above).

Hemoglobin is the most effective buffer against invading carbonic acid, for several reasons. The enzyme carbonic anhydrase, which remarkably catalyzes the reversible reaction between CO<sub>2</sub> and water, is confined with hemoglobin in the erythrocyte. Because CO<sub>2</sub> is so rapidly diffusible, practically all of the H<sub>2</sub>CO<sub>3</sub> formed from CO<sub>2</sub> in the tissues arises within the red cell. When hemoglobin is deoxygenated in the tissues, it becomes a relatively weaker acid, thus converting much of the accumulating H<sub>2</sub>CO<sub>3</sub> into bicarbonate ion within the erythrocyte. The requirements of the Donnan equilibrium are met by an exchange between some of this extra bicarbonate in the cell, and chloride ion in the plasma. Thus the bicarbonate concentration in plasma rises somewhat as the CO<sub>2</sub> tension (hence, H<sub>2</sub>CO<sub>3</sub>) also rises, and consequently little change in plasma pH occurs. The over-all effect is that most of the CO<sub>2</sub> arising

in tissues is converted into bicarbonate ion (i.e., buffered), and the increment of hydrogen ions resulting because buffering is not a perfect defense is largely trapped within the erythrocyte. In addition, a modest fraction of CO<sub>2</sub> combines directly with hemoglobin protein to form the carbamino derivative, a form in which some CO<sub>2</sub> is transported from the periphery to the lungs.

If we take pH 7.0 as representing one of the limits of hydrogen-ion concentration compatible with life, then the physiologically available buffer capacity may be defined in terms of the quantity of strong acid required to bring about a decline in pH from 7.4 to 7.0. It is found that in the circulating blood alone the physiologically available buffer capacity amounts to about 150 ml. of 1 N strong acid, of which about 65 per cent is buffered by the bicarbonate system, 30 per cent by the hemoglobin system, and the remaining 5 per cent by serum proteins, the phosphate system, etc. Indirect measurements indicate that the physiologically available buffer capacity of the extravascular compartments is about five times that of the blood, so that the equivalent of some 800 to 1000 ml. of 1 N strong acid may be neutralized at the expense of a decline in serum pH of 0.4. Such considerations indicate clearly the degree to which acid-base balance is dislocated in a patient when accumulation of strong acids has decomposed some 80 per cent of the bicarbonate and has driven the pH down to 7.1, and indicate the metabolic or renal load imposed in the course of the return of the balance to its normal status.

During health the composition of body fluids in the various compartments remains rather constant. It follows that the buffer systems are continuously being restored to their normal state, in terms of quantities and values of their salt/acid ratios, by processes which result in the elimination from the body of the relatively stronger acids which were neutralized (buffered). This elimination takes place in terms of the excretion of an acid urine containing free organic acids and monobasic phosphate as buffer pairs in which the salt/acid ratios are smaller than those in the plasma ultrafiltrate from which the urine was formed. In addition, the anions of these acids, sulfate, and other acidic end products are excreted in variable proportions as ammonium salts rather than as alkali salts, and the formation of ammonium ion from ammonia involves the elimination from the internal environment of one hy-

Table 30  
NORMAL ELECTROLYTE COMPOSITION OF BLOOD PLASMA

Constituent	Plasma Concentration			
	Milliequivalents per Liter	Mg. %	Other Concentration Terms	Base Equivalence (mEq.)
Sodium.....	138 -145	..	..	..
Potassium.....	4.1- 5.6	16 - 22	..	..
Calcium.....	4.5- 5.5	9 - 11	..	..
Magnesium.....	0.8- 2.5	1 - 3	..	..
Bicarbonate ( $\text{CO}_2$ cap.).....	24.6- 32.1	..	55-72 vol. %	..
Chloride.....	98 -104	575 -610 (as $\text{NaCl}$ )	..	..
Phosphate.....	1.7- 2.3	3 - 4	..	..
Sulfate.....	0.3- 0.7	0.5- 1.1	..	..
Organic acids.....	..	..	..	..
Protein.....	..	..	6-8 Gm./100 ml.	5 - 7 14.6-19.

drogen ion; i.e., excretion of the ammonium salts eliminates both the anion and cation (hydrogen ion) of the original acid. Further, direct tubular secretion of hydrogen ions permits the exchange of these for alkali cations, thus permitting still further acidification of the urine. These processes also conserve the alkali cations which would otherwise be lost.

Carbonic acid usually is eliminated almost entirely via the lungs as carbon dioxide. Elimination as bicarbonate via the urine is negligible except when the diet has an alkaline residue, during alkalotic states, or, rarely, as a result of renal tubular dysfunction. Normally, this mechanism can provide nicely for the saving of chloride ion; i.e., excess alkali cation may be rid from the body as bicarbonate salts without wastage of chloride.

It follows from these considerations that disturbances in the status of buffer systems—that is, alterations in acid-base balance—occur as the result of three general causes: (1) The rate of production or intake of acidic or basic metabolites becomes accelerated so that otherwise normal excretory processes cannot adequately dispose of the increased load (diabetic ketosis). (2) The excretory processes themselves are impaired so that there is deficient or excessive elimination in face of either a normal or increased load (uremia). (3) Uncontrolled, abnormal kinds of elimination of water and electrolytes occur (vomiting, diarrhea). Inseparably linked with changes in the composition of body fluids brought about by these means are the changes in volume, the main

features of which are discussed elsewhere (Chapter 28).

The composition of blood plasma in terms of electrolytes is illustrated in figure 33 and table 30. In addition, for comparison, the compositions of interstitial and intracellular fluids are also given. Plasma and interstitial fluid are quite similar, the slight differences being predictable as a consequence of the Donnan effect due to differences in the quantity of the nondiffusible constituent, protein. Interstitial fluid and intracellular fluid, although in osmolar equilibrium, have quite different electrolyte patterns. The effects of acid-base distortions on the composition of plasma and interstitial fluid are well understood, but the corresponding effects upon intracellular fluid composition are as yet imperfectly known. Inasmuch as deductions concerning acid-base balance are usually made from data involving plasma analyses, the problem may be discussed largely from the standpoint of plasma compositional changes, providing it is remembered that these, along with volume changes, are reflected in alterations in the other compartments.

It should be noted that about nine tenths of the total alkali cation in plasma is sodium. Ordinarily, chloride constitutes about two thirds of the sum of the anions, bicarbonate slightly less than one fifth, and protein approximately one tenth. Inasmuch as carbon dioxide is continuously produced by metabolic processes, with most of it being converted into bicarbonate ion, there

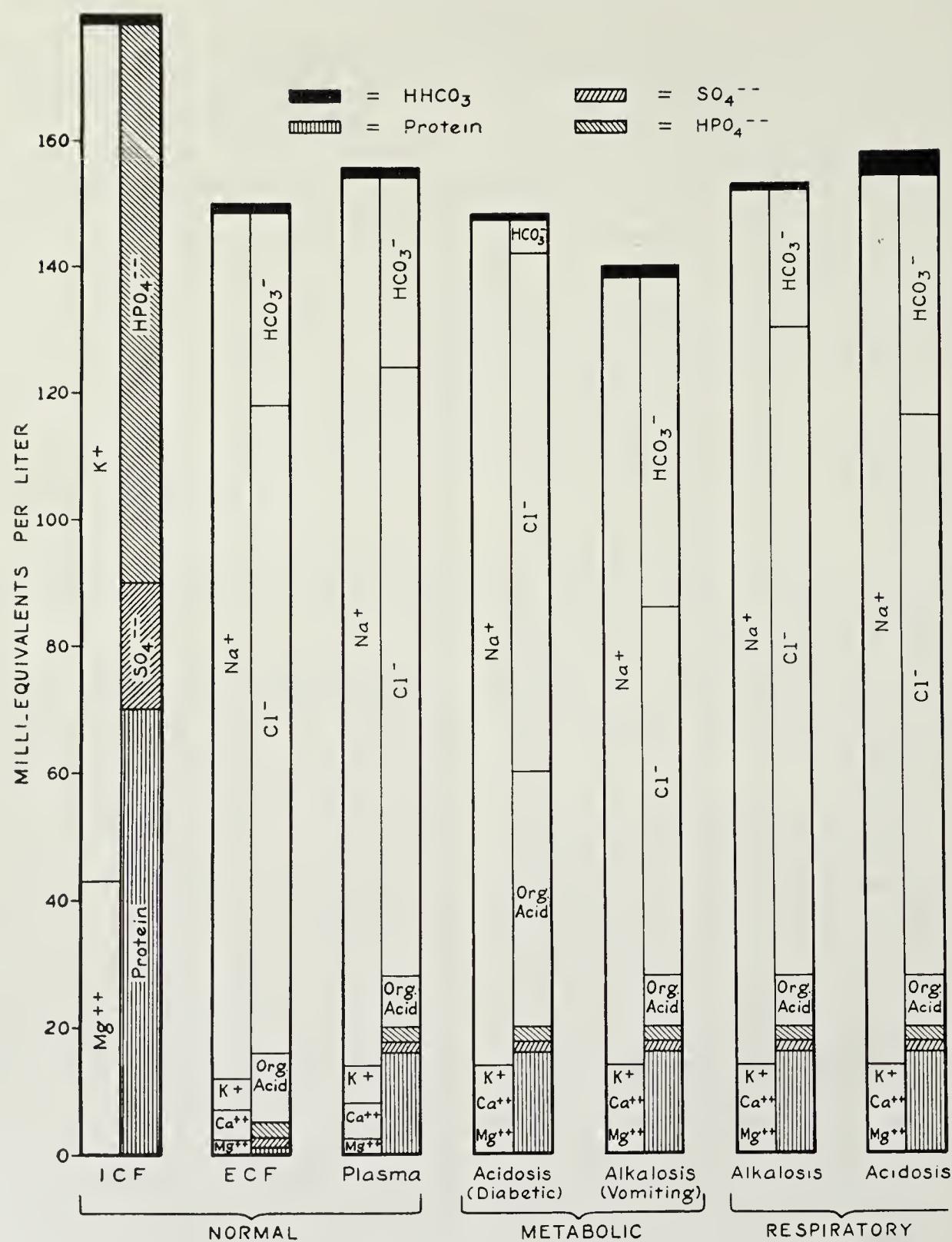


FIG. 33. Electrolyte composition of body fluids and alterations induced by acidosis and alkalosis.

This figure is modeled after those of Gamble. The three columns at the left indicate the electrolyte composition of intracellular fluid, extracellular (interstitial) fluid, and blood plasma, respectively. The important points are the predominance of potassium, magnesium, and phosphate in the intracellular fluid, and the striking similarity of interstitial fluid and blood plasma, except for the higher protein content of the latter.

The four columns at the right illustrate the alterations in blood plasma in some of the most important types of acid-base disturbance. (In constructing these columns, alterations in potassium, magnesium, calcium, sulfate, phosphate, and protein have been neglected.) Note especially that: (1) Metabolic acidosis, of the type illustrated, is characterized by primary increase in organic acid, with secondary reduction of bicarbonate, compensatory loss of carbonic acid (increased ventilation), and compensatory excretion of chloride. (2) Metabolic alkalosis due to vomiting is characterized by primary chloride deficiency, with secondary rise in bicarbonate and compensatory retention of carbonic acid. (3) Respiratory alkalosis is characterized by primary loss of carbon dioxide (hyperventilation), with compensatory excretion of bicarbonate and compensatory retention of chloride. (4) Respiratory acidosis is character-

(Continued on facing page.)

is an essentially limitless reserve of bicarbonate ion, providing the buffer salts are available to permit the conversion. The excretion of carbon dioxide, then, is readily altered by pulmonary ventilational changes, or by changes in rate of urinary excretion of alkali bicarbonate. There is, however, no reserve of chloride, but the flexibility of the fate of CO<sub>2</sub> permits considerable fluctuation in the relative concentrations of bicarbonate and chloride, without any necessary alteration in the sum of the two. This reciprocal relationship between chloride and bicarbonate constitutes an important mechanism of adjustment whereby the total electrolyte concentration may remain undisturbed in spite of distortion in anion pattern.

In the case of the bases of the plasma no such reciprocal relationship exists, and the total concentration of alkali cations is essentially a function of the sodium concentration. Since under all conditions compatible with life the sums of the alkali cations and anions are, for practical purposes, equal, it becomes evident that during health the sum of the chloride and bicarbonate concentrations is proportional to the sodium concentration. In the presence of disease the accuracy of this approximation is conditioned by the possibility of other anions being present in excess of normal—e.g., phosphate, sulfate, and organic acids. Hence, in all such instances, this indirect assessment of the total base concentration by determination of chloride and bicarbonate must be made with great caution.

It should be emphasized that three things must be known in order to obtain an accurate evaluation of the acid-base status of a patient. These are the alkaline reserve (bicarbonate content of extracellular fluid), the hydrogen-ion concentration or pH, and the volume of body fluids. The total CO<sub>2</sub> content of serum or plasma, or the CO<sub>2</sub> combining power of either, constitutes an adequate measure of the alkaline reserve; i.e., the total CO<sub>2</sub> content or CO<sub>2</sub> combining power indicates whether or not the alkali buffer salts are present in normal concentrations. (The total CO<sub>2</sub> content determines CO<sub>2</sub> present as both H<sub>2</sub>CO<sub>3</sub>

and BHCO<sub>3</sub> in the circulating plasma [usually venous]; the CO<sub>2</sub> combining power is a measure of the CO<sub>2</sub> present as BHCO<sub>3</sub>, as calculated from the total CO<sub>2</sub> content of serum or plasma separated from whole blood [usually venous] and re-equilibrated with an air-CO<sub>2</sub> mixture in which the pressure of the CO<sub>2</sub> is equal to that of the normal alveolar CO<sub>2</sub> tension—i.e., about 38 mm. Hg. The value obtained is usually about 3 vol. % higher than the corresponding total CO<sub>2</sub> content, a difference which is unimportant for those purposes for which CO<sub>2</sub> combining powers are obtained.)

The pH of serum or plasma may be determined directly by electrometric methods, or may be calculated with the aid of the Henderson-Hasselbalch equation from measurement of (1) the total CO<sub>2</sub> content, and (2) the alveolar CO<sub>2</sub> tension, from which in turn the carbonic acid concentration [H<sub>2</sub>CO<sub>3</sub>] may be calculated, with the aid of the Bohr solubility coefficient for carbon dioxide in serum (0.51 at 38° C.).

The volume of body fluids is not so readily measurable, but may be approximately assessed by clinical observation (Chapter 28).

In most circumstances, fortunately, the measurement of the alkali reserve alone gives the necessary information concerning the acid-base status, and the corresponding direction of the pH change from normal may be inferred upon the basis of collateral information, including that obtained by observation, from the history, and examination of the urine (see below).

**Classification of Acid-Base Disturbances.** These disorders may be divided into two general groups, "gaseous" (or respiratory) and "metabolic," according to whether the primary disturbance as reflected in the salt/acid ratio of the bicarbonate buffer system is in the concentration of the bicarbonate as a result of a metabolic dislocation, or the carbonic acid as a result of a primary disorder of the respiratory mechanism. Table 31 summarizes the subdivisions and main features of these groups.

It is a feature of acid-base regulation that disturbance in the absolute concentrations of one of the members of buffer pairs is followed by ad-

FIG. 33—(Continued)

ized by primary retention of carbon dioxide (diminished ventilation), with compensatory retention of bicarbonate and compensatory increase in chloride excretion. (5) The striking tendency of sodium, the chief determinant of osmolar concentration in extracellular fluid, to remain constant despite widespread alterations in other components illustrates the general principle that the body tends to preserve osmolar concentration, even at the expense of compositional changes.

*Table 31*  
CLASSIFICATION OF ACID-BASE DISORDERS

<i>Types of Disturbances</i>			<i>Direction of Change in*</i>					
			<i>H<sub>2</sub>CO<sub>3</sub></i>	<i>BHCO<sub>3</sub></i>	<i>Salt/Acid Ratio</i>	<i>Serum pH</i>	<i>CO<sub>2</sub> Combining Power</i>	<i>Urine pH (If Renal Function Is Normal)</i>
Respiratory	Primary CO <sub>2</sub> excess (acidosis)		Increase	Increase	Decrease	Decrease	Increase	Decrease
	Primary CO <sub>2</sub> deficit (alkalosis)		Decrease	Decrease	Increase	Increase	Decrease	Increase
Metabolic	Primary alkali excess (alkalosis)	Alkali retention	Increase	Increase	Increase	Increase	Increase	Increase
		Acid loss	Increase	Increase	Increase	Increase	Increase	Increase
	Primary alkali deficit (acidosis)	Alkali loss	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease
		Acid retention	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease

\* Those changes in [H<sub>2</sub>CO<sub>3</sub>], [BHCO<sub>3</sub>], and CO<sub>2</sub> combining power which are secondary—i.e., compensatory changes—are *italicized*. It should be understood that these tend to minimize the alteration in salt/acid ratio and pH produced by the primary disturbance. (See subsequent discussion.)

justments which tend to alter the concentration of the other members, so that the value of the salt/acid ratio, and hence the pH, remains more nearly normal than would otherwise be the case. The degree to which these "compensatory" adjustments may take place differs considerably among the different types of disturbances. For example, in both types of gaseous disorders, the compensation may often be almost complete. Thus primary CO<sub>2</sub> excess brought about by any mechanisms which decrease the rate of elimination of carbon dioxide via the lungs is shortly followed by the urinary excretion of excessive amounts of chloride and a corresponding increase in serum [BHCO<sub>3</sub>], which is reflected in a rising CO<sub>2</sub> combining power. The initial fall in pH is thus followed by a return toward the normal range. Exactly the opposite series of events accompanies and follows the onset of primary CO<sub>2</sub> deficit. These adjustments occur as described, however, only if the kidneys, which are largely responsible, are functioning in their normal manner.

In the case of the metabolic disturbances, the compensatory adjustment is largely the result of stimulation or depression of the respiratory center, with corresponding alterations in the abso-

lute concentration of [H<sub>2</sub>CO<sub>3</sub>]. The degree of compensation rarely approaches completeness in even chronic states, as a considerable stimulus in terms of the primary defect is necessary to affect the respiratory mechanism. In addition, it is a common tendency of the metabolic disturbances to exhibit progressive decompensation, inasmuch as the primary process is so often slowly or rapidly progressive—e.g., disorders of renal function and untreated diabetic acidosis. Furthermore, the respiratory act itself is mechanically limited in the degree to which it may lower the alveolar CO<sub>2</sub> tension, while anoxia becomes a limiting factor in the degree to which this tension may be raised by diminution in respiratory exchange.

Of the subdivisions of the metabolic group, *alkali excess due to alkali retention* is the least common. It arises in most instances when excessive amounts of alkalies, such as bicarbonates and carbonates, have been taken or administered, and especially when renal function is impaired. The rapid disposal of the organic portion of certain alkali salts of organic acids (e.g., sodium lactate) may also precipitate alkalosis due to alkali retention. Inasmuch as the excretion of sodium salts by the kidneys is a relatively slow process,

retention of ingested fluid manifested by edema often accompanies this disorder.

*Alkali excess as a result of acid loss* is a much more common occurrence because of its relation to vomiting. The rate at which the dislocation develops is a function of the amount of vomitus and its hydrochloric acid content. Because, in this instance, fluid as well as variable amounts of base (mostly sodium) are lost with the vomitus, this type of alkalosis is quite apt to be accompanied by a decline in extracellular fluid volume as well as by hypochloremia. If the vomitus contains little free hydrochloric acid, alkalosis does not occur, but rather acidosis as the result of excess formation of ketone acids (starvation) and acid retention consequent to inadequate renal function (Chapter 19). Even when severe alkalosis has developed, this may be greatly modified by such factors and, indeed, may revert to acidosis. It should be noted that severe dehydration, even when accompanied by alkalosis, may actually be associated with a reduction in the physiologically available alkali because of the large loss of interstitial fluid.

*The alkali deficits* comprise the vast majority of acid-base disturbances. In the case of *alkali deficit due to the retention of acid*, the decline in CO<sub>2</sub> combining power is the direct consequence of the conversion of the buffer salts to salts of the stronger acids concerned. In the plasma this results in a smaller quantity of sodium ion being available to balance bicarbonate ion, a decline in the bicarbonate/carbonic acid ratio, and hence a fall in pH. The extent of the latter is minimized to the degree that the H<sub>2</sub>CO<sub>3</sub> concentration is decreased by increased respiratory activity. The loss of water and sodium in the excretion of these acids results (unless replaced) in a decline in extracellular fluid volume which, if profound, will precipitate renal failure and exaggerate the retention observed.

In states of disordered renal function in which an acid urine cannot be formed of sufficient degree to conserve base adequately, extracellular fluid deficit develops; and if the clearance of solutes falls to the point of retention of organic acids, phosphate, and sulfate, then a corresponding reduction is observed in the CO<sub>2</sub> combining power.

*Alkali deficit due to alkali loss* may be the consequence of failure of the kidney to conserve base, or may be due to loss of alkaline secretions from

the gastrointestinal tract—for example, from fistulas or with diarrhea. Such loss initially results in extracellular fluid deficit due to the fluid and base thus eliminated. The renal elimination of chloride (in part as the ammonium salt) tends to prevent distortion of the serum and interstitial fluid electrolyte pattern, but as the dehydration becomes more severe, diminished ammonia formation followed by excretory failure of the kidney superimposed upon excessive ketone production—if there is concomitant starvation—results in the retention of acids, with the precipitation of severe acidosis.

It is seen that the separation of types of alkali deficit is not sharp, and that they are usually co-existent at those times when the CO<sub>2</sub> combining power has seriously declined. The fact that primary alkali loss is usually initiated by processes which cause decline in the volume of body fluids, and hence initially does not materially alter the CO<sub>2</sub> combining power, is deceptive because actually the physiologically available alkali in terms of the acid the organism may subsequently tolerate has been reduced, and the further retention of relatively smaller masses of acid substances produces marked acidosis.

*Primary CO<sub>2</sub> deficit* is by far the most commonly observed gaseous type of acid-base balance disorder. Any condition which causes pronounced hyperventilation may lead to alkalosis. Emotional disturbances are common causes, and other precipitating factors include lesions of the brain stem and hyperthermia. The immediate consequence of CO<sub>2</sub> deficit is an increase in pH (i.e., alkalosis), without material alteration in the CO<sub>2</sub> combining power or total CO<sub>2</sub> content other than the minor alteration consequent to the accompanying chloride-bicarbonate shift between plasma and erythrocytes. Subsequently, however, the renal elimination of bicarbonate and retention of chloride tends to reduce the CO<sub>2</sub> combining power in the course of achieving a compensated state. The alkali reserve, then, tends to be diminished despite an alkaloic state, and if sole reliance is placed upon measurement of the CO<sub>2</sub> combining power, the erroneous conclusion may be drawn that there is an acidosis. This error may be avoided by the demonstration of large amounts of bicarbonate in the urine (i.e., the urine is alkaline). In those instances where there is reason to believe renal function is inadequate, direct determination of serum pH is ad-

visable, as the urine may be found to be neutral or faintly acid in spite of systemic alkalosis.

*Primary CO<sub>2</sub> excess* occurs as the result of advanced pulmonary disease or following the administration of respiratory depressant drugs—for example, morphine. The immediate result is a decline in pH—that is, acidosis—without significant alteration in CO<sub>2</sub> combining power other than that increase due to movement of the chloride ion into the erythrocytes. Subsequent compensatory adjustments involve renal elimination of chloride, with a decrease in sodium chloride and an increase in serum BHCO<sub>3</sub>, so that in this instance there is acidosis of varying degrees of compensation in the presence of a rising alkali reserve. Again a false conclusion as to the nature of the disorder may usually be avoided by the demonstration of an acid urine, although if renal function is inadequate this may not be conclusive, and in the absence of conclusive evidence in terms of history and physical signs, the direct determination of serum pH may be necessary.

Two features of the gaseous types of acid-base upset are rather striking. The first is the degree to which they tend to compensate, which in chronic states may be sufficiently complete so that the serum pH is within the normal range. The second is that these disorders are not attended by the marked alterations in volumes of body fluid compartments so characteristic of the metabolic disorders.

**Clinical Manifestations of Acid-Base Disturbances.** The clinical picture of patients presenting serious disturbances of acid-base equilibrium may be divided into three parts:

1. Manifestations of the primary disease process. These naturally vary according to the nature of the underlying disorder.

2. Manifestations of the frequently associated disturbance in volume of body fluids. When the disorder responsible for the acid-base disturbance is mild, there may be no disorder of fluid balance. This is especially observed in the gaseous types of dislocation. When metabolic acidosis or alkalosis due to acid loss is severe, there is commonly associated loss of fluid and sodium salts along with the acids removed from the body, and this leads to a state of extracellular fluid deficit. The manifestations of such a state may dominate the picture (Chapter 28).

3. Manifestations of the acid-base disorder per se. For reasons which have been mentioned, these

are frequently in the background. When alkalosis is severe and uncompensated, tetany (due to central nervous system hydrogen-ion deficit, not peripheral calcium-ion deficit) in the form of muscular twitchings and spasm may be present. More commonly, the milder symptoms of alkalosis, consisting of numbness in the distal portions of the extremities and in the face, with paresthesia and a "drawing" sensation in these parts, are found. In hyperventilation alkalosis, palpitation, abdominal distention and belching are common components of the seizures, accompanied by anxiety out of all proportion to the seriousness of the condition. In some instances there is only the complaint of recurrent "weak spells" (Chapter 7) initiated by a feeling of inability to get a deep breath. In severe alkalosis of metabolic origin, respiration may or may not be noticeably altered.

Outspoken acidosis is frequently accompanied by a characteristic type of breathing, the respiration being increased in depth, with sighing, and only a moderate increase in rate (Kussmaul breathing). This type of respiration is rarely observed in patients in whom the CO<sub>2</sub> combining power has not declined to less than half of the normal value, and, hence, points at once to a severe diminution of alkali reserve. With further increase in the severity of the acidosis the respiratory responses may diminish as the mechanism of breathing becomes exhausted.

## ALTERATIONS IN CHLORIDES

**Excess of chloride concentration** in the extracellular fluid is sometimes induced by the administration of sodium chloride, parenterally, as the sole source of fluid to patients who for one reason or another are not taking water by mouth. Under such circumstances it is accompanied by an excess of sodium, and the clinical picture is essentially that already described (Chapter 28) as an excess of extracellular fluid which may be accompanied by a deficit of intracellular fluid. Less commonly, hyperchloremia is the result of disease of the renal tubules, with diminished excretion of chloride. The resulting acidosis tends to draw calcium from the bones and to increase the concentration of calcium in the urine, thus predisposing to renal stones and renal calcification. Mild hyperchloremia is observed in compensated gaseous alkalotic states and, in connection with residence at high altitude, may be considered physiologic.

**Deficiency in chloride** is usually the result of excessive loss of chloride from the body, and the clinical picture so induced depends upon whether or not sodium is likewise lost, and also upon the volume of the water intake. When there is deficit in chloride as the result of excessive loss via the urine or from the gastrointestinal canal, variable amounts of sodium are also lost, and the patient is likely to be seriously ill and to drink relatively little water. The picture induced is, therefore, primarily that of deficiency of extracellular fluid volume, as discussed in the previous chapter.

The most common cause of chloride deficit in seriously ill patients is vomiting. Under these circumstances there is likely to be a deficiency of water because the act of vomiting prevents drinking water. However, since the gastric juice, if it is strongly acid, is poor in sodium as compared to chloride, there may be little or no sodium deficiency. As the chloride is lost from the blood into the gastric juice, and thence from the body, a condition of alkalosis develops with the rapid substitution of bicarbonate for chloride. This leads to depression of alveolar ventilation, with gradual retention of  $\text{CO}_2$  as  $\text{H}_2\text{CO}_3$ . The clinical picture induced is that of alkalosis accompanied, when uncompensated, by tetany, and associated with characteristic alterations in the composition of the blood—i.e., diminution in chloride, increase in bicarbonate, and, as the extracellular fluid deficit becomes profound, increase in non-protein nitrogen. Although, theoretically, such a state might best be treated by the administration of hydrochloric acid, or ammonium chloride (which is equivalent to giving hydrochloric acid, since much of the ammonium ion is rapidly converted into urea in the liver), in the absence of renal shutdown it is usually sufficient to administer sodium chloride because as soon as chloride and fluid are made available the kidney rapidly removes the excess sodium by excreting this along with bicarbonate. This is one of the few situations in which the administration of sodium chloride solution is preferable to the administration of a balanced electrolyte solution consisting of the chloride and bicarbonates of sodium and potassium.

When, as is not uncommonly the case, chloride deficit is the result of sweating, it is likely to be accompanied by corresponding sodium deficit; but under these circumstances the patient—usually a healthy individual performing physical

labor in a hot environment—is likely to drink water abundantly. The symptoms induced, therefore, are not directly the result of the chloride deficit, or even of the sodium deficit, but are to some extent to be referred to the state of relative water excess—i.e., to a diminished osmolar concentration in the extracellular fluid and, as the result of shifts in water, to a change in osmolar concentration in the intracellular fluid. The clinical picture is that of stoker's cramps, or miner's cramps, and this state has likewise been discussed in a previous chapter. It can be prevented by increasing the intake of salt in individuals who sweat excessively, and can be rapidly treated successfully in the administration of concentrated sodium chloride, either orally or parenterally.

The chloride deficit observed in patients with lobar pneumonia deserves special mention, in that it is the summation of at least three factors. These are: (1) shift of chloride into erythrocytes secondary to  $\text{CO}_2$  retention; (2) local accumulation of sodium and chloride in the pneumonic process; and (3) loss of sodium and chloride in sweat. Only the deficit due to the latter mechanism should be treated in terms of salt administration.

### ALTERATIONS IN POTASSIUM

Although this is the most abundant cation in the body, relatively little is known about its function. Potassium plays an important role in the maintenance of the osmolar concentration of intracellular fluid in a manner somewhat analogous to that of sodium in regard to the extracellular fluid. The cell membranes of tissues are relatively impermeable to potassium and sodium, so that potassium is held in the intracellular space, whereas sodium stays in the extracellular compartment. Such movement of potassium out of cells, or sodium into cells, as does occur to a slight extent under certain circumstances, appears to take place rather slowly. The potassium ion is important in regard to neuromuscular transmission, and is concerned in the maintenance of the normal conduction and contraction of the heart. In so far as the last two functions are concerned, potassium and calcium appear to be antagonists, and it is believed that proper balance between the two is perhaps more important than the exact concentration of either. Potassium is also important in carbohydrate metabolism, although its exact role in this regard remains to be

clarified. Carbohydrate utilization, with rapid deposition of glycogen, is accompanied by a decline in the concentration of potassium in extracellular fluids similar to that observed for inorganic phosphate.

Before considering alterations in concentration of potassium in the body, it will be worth while to mention some of the states in which there is a change in the over-all turnover of potassium, without any alteration in its concentration in serum and extracellular fluid. The excretion of potassium in the urine of the adult is normally equivalent to that taken in with the food, and since different foods vary markedly in their potassium content, wide variations in urinary excretion are compatible with health.

Whenever, for any reason, there is a change in the mass of body protein, such a change is reflected in the excretion of urinary potassium, but without any significant change in potassium concentration in the blood. Thus, when the body protein is being catabolized rapidly, as during fever and starvation, potassium excretion increases as the utilization of cellular protoplasm liberates, in some way, a corresponding fraction of intracellular potassium into the extracellular space. Similarly, when protein balance is being restored—as during convalescence after wasting illnesses—the urinary potassium may drop to low levels unless there is a corresponding increase in the potassium intake.

Excessive fatigue of either cardiac or skeletal muscle tends to lead to loss of potassium from these structures, such loss being temporary and being rapidly replaced during recovery.

**Deficiency of potassium** in the plasma (and extracellular fluid), brought about largely by shift of extracellular potassium into the intracellular compartment, occurs in individuals with familial periodic paralysis. This rare disorder produces recurrent attacks of profound muscular weakness, the symptoms being improved rapidly by the administration of potassium salts. In certain types of renal disease characterized by retention of chloride, there may be an associated decline in serum potassium, with consequent episodes of pain in the extremities, and paralysis. When potassium deficiency is suspected as a cause of recurrent episodes of muscular weakness, and when determinations of potassium are not readily available, the electrocardiographic dem-

onstration of marked decline in voltage of the T waves will constitute strong, although indirect, evidence; and more particularly so if the T wave abnormality, as well as the muscular weakness, disappears promptly following the administration of potassium salts.

Potassium deficit in the extracellular fluid may occur whenever there is rapid passage of glucose into the cells, this being accompanied also by a decline in the concentration of inorganic phosphate. This may occur during the management of diabetic coma. Another important cause of potassium loss is the urinary excretion of the potassium (as well as the sodium) salts of ketone acids. During severe diarrhea there may be a marked loss of potassium into the stools. Recent work suggests that under such circumstances the deficiency of potassium in the extracellular fluid may have serious consequences. It is, therefore, important in the management of patients with these disorders to administer fluids which contain potassium as well as sodium.

More common, but less dramatic, as a cause of potassium deficit in the body fluids, is the administration of potassium-free fluids to patients, and especially so when the individual already has a deficit of intracellular fluid. The fluids commonly used for parenteral administration are potassium-free, and since the osmolar concentration within the cell depends to a great measure upon the potassium concentration, it may be impossible to overcome properly a state of intracellular fluid deficit unless the administered fluid contains salts of potassium as well as of sodium. The symptoms of potassium deficit in the cells are essentially those of intracellular fluid deficit (Chapter 28). Of these, the most important are weakness and stupor.

The continued administration of excessive quantities of desoxycorticosterone may induce a potassium deficit. As the pharmacologic actions of potassium are related not only to the absolute concentration, but also to the sodium/potassium ratio, the concomitant sodium retention may increase the sodium concentration so that the effects of potassium deficit are augmented.

**Potassium Excess.** The normal kidney has the power to excrete urine rich in potassium, in response to slight increments in plasma level of this substance. Hence, no well-marked excess of potassium in the plasma can occur in the presence of normal renal function. When, as the result of

the catabolism of body protein or of disturbance in fluid balance, there is a passage of potassium from the cells into the extracellular fluid, a small increase in the plasma level of potassium may occur, but such increase is minimized by the more rapid renal excretion of potassium. Hence, although in states of extracellular fluid deficiency there may be some shift of water and potassium from the intracellular space into the extracellular compartment, the rise in serum potassium is minimized because the excess of this substance in the extracellular fluid is quickly excreted unless the fluid deficit is sufficiently severe to cause depression of renal function.

The capacity of the kidney to excrete potassium appears to be regulated to some extent by the adrenal glands. In the presence of well-marked adrenal cortical insufficiency there is, in association with rapid decline of plasma volume, a rise in extracellular potassium. The effects of this are augmented by any deficit in sodium concentration which may coexist.

Occasionally, increased levels of potassium in the plasma are encountered in states of renal insufficiency. In patients with outspoken uremia the potassium level may be normal, but is frequently elevated. Such elevation is most apt to be observed in patients with severe oliguria or anuria. There is considerable evidence that the development of the cardiac arrhythmias, and of the well-marked changes in the configuration of the electrocardiogram so common in these uremic patients, is related to this excess of potassium. Since the changes observed in the T waves and in the initial ventricular complex may be similar to those sometimes encountered following myocardial infarction, errors in diagnosis may be made, unless the clinical picture and the chemical findings are considered as well as the electrocardiographic pattern.

Excess of potassium may be one factor in the production of the twitchings and convulsions commonly seen in the uremic state. Such an excess of potassium is more effective in the presence of the calcium-ion deficiency which commonly exists in such patients.

It has been shown that patients with acute peripheral circulatory failure commonly exhibit an elevation of serum potassium, and the suggestion has been offered that such an increase may be of primary importance in the pathogenesis of the circulatory failure. However, the evidence

would seem to indicate that the potassium excess is the result and not the cause of the manifestations of "shock." Under such circumstances the increase in serum potassium may be brought about by several mechanisms, one of them being the extracellular fluid deficit with consequent shift of potassium and water from the intracellular compartment, another being deficient renal excretion as the result of diminished renal blood flow, a third being rapid destruction of extravasated red blood corpuscles, and a fourth being increased protein catabolism. Whether, in patients with Addison's disease, the increase in serum potassium is to be ascribed entirely to the peripheral circulatory failure secondary to loss of sodium and water from the extracellular space, or whether under such circumstances increase in serum potassium is due to a specific deficiency of adrenal cortical substances which normally control the renal excretion of potassium, is uncertain at present, although considerable evidence seems to support the latter interpretation.

## CALCIUM AND PHOSPHORUS

Since these two elements are closely interrelated in their behavior in the body, they will be discussed together.

Most of the calcium of the body is contained in the bones, but the small amount present in body fluids exerts important physiologic effects. One of the most important of these relates to the nervous system and to neuromuscular transmission. Deficiency of calcium produces marked increase in neuromuscular irritability, with twitchings (tetany) and, in advanced stages, convulsions. Similar effects may be induced experimentally by the intracisternal administration of substances, such as phosphate and citrate, which form un-ionized calcium salts, and which thereby reduce the amount of ionized calcium in the cerebrospinal fluid. This type of tetany must be clearly distinguished from that associated with alkalosis (e.g., hyperventilation), in which calcium does not play a significant role.

Another important effect of calcium in the tissue fluids relates to the heart, the effects here being essentially the reverse of those of potassium, which have been mentioned already. There is likewise considerable evidence that calcium is concerned in the permeability of capillary and cell membranes, but thus far no clear-cut rela-

tionship between this property and clinical medicine has been demonstrated.

Phosphorus, likewise, has multiple functions. Aside from its importance as a constituent of the complex apatite comprising the mineral of bone structure, phosphorus is a component of the complex molecules which constitute the chief negative ions in the intracellular space, and it is contained in certain fatty derivatives, the phospholipids. The great importance of phosphate bond energy and of phosphorylation processes in metabolism will be discussed subsequently (Chapter 30). Phosphorus is also intimately involved in the mechanisms for maintenance of normal acid-base balance. As an electrolyte component of the extracellular fluid and urine, phosphorus is almost entirely in the form of the ions of the monobasic and dibasic salts of orthophosphoric acid. The proportions vary with the pH of the environment and may be calculated by employment of the Henderson-Hasselbalch equation.

**State of Calcium in Body Fluids.** The intracellular fluid normally contains little or no calcium, but the blood serum has a total concentration which normally does not vary beyond the limits of 9 to 11 mg. % (= 4.5 to 5.5 mEq. per liter). A very small portion of the total serum calcium is in the form of the colloidal salts of phosphate, citrate, and other un-ionized calcium salts. A much larger fraction, amounting normally to about one half of the total, is present as a nondiffusible un-ionized calcium-protein complex. The amount of calcium in this state depends upon the concentration of the plasma proteins, and especially upon the albumin fraction. The remaining portion of the total calcium exists as diffusible ionized calcium ( $\text{Ca}^{++}$ ) normally amounting to about 5 mg. %. It is only the ionized fraction which is physiologically active, and its concentration appears to be primarily controlled, in terms of maintenance of constancy, largely by the secretion of the parathyroid gland. Alterations in concentration of the ionized fraction occur as a result of changes in the activity of the parathyroid, or secondary to factors affecting absorption and excretion with which the parathyroid regulatory activity cannot keep pace. Inasmuch as interstitial fluid contains little protein, almost all of its calcium is in the ionized form.

It follows from these considerations that determinations of total serum calcium are relatively meaningless unless interpreted in relation to the

concentration of serum proteins. This relationship has been formulated in terms of nomograms dealing with the relationships between total serum calcium, ionized serum calcium, and serum proteins, so that the ionized fraction is readily estimated when only total calcium and serum protein have been determined.

The total serum calcium also bears a relation to the concentration of inorganic phosphate, which is in most instances an inverse one. The reasons for this are not entirely understood. In any event, marked increases in serum inorganic phosphate are usually accompanied by a diminution in the ionized as well as the total serum calcium.

**Vitamin D in Relation to Calcium and Phosphorus.** The chief function of the natural vitamin D group of substances appears to be that of promoting the absorption of calcium from the gastrointestinal tract. Deficiency of this vitamin, therefore, leads to defective mineralization of the bones, and to the clinical states of rickets (children) or osteomalacia (adults). It is now generally recognized that the several D vitamins are concerned in functions in addition to the absorption of calcium. Thus it appears that they exert differing degrees of influence upon the mechanisms promoting deposition of bone at the epiphyseal provisional zone of calcification, and at the same time promote resolution of bone from other areas. In addition, the maximum rate of phosphate reabsorption by the tubules is increased by administration of the vitamin. Whether this is a direct effect, or is secondary to a depressant effect of the vitamin on the parathyroid gland, appears to be uncertain, for there is some evidence that the direct renal effect may be that of increased phosphate excretion. Effects upon over-all phosphate excretion are the result of the summation of at least these actions, the collateral influences of the parathyroid hormone and the quantity of phosphate and calcium in the diet.

**Parathyroid Gland in Relation to Calcium and Phosphorus.** The hormone produced by these glands appears to have effects qualitatively similar to those of vitamin D. However, here, the effect on calcium absorption from the gastrointestinal tract is the less important one, and the quantitatively more striking effect is that of increasing the renal excretion of phosphate. The decline in plasma phosphate so induced leads to

the release of phosphate from bone and, with it, the release of calcium. The plasma calcium therefore rises, and this effect, particularly pronounced following administration of large doses of parathyroid hormone, or in hyperparathyroidism, is ordinarily considered the most important one, although the available evidence indicates that it is in large part secondary to the stimulation of phosphate excretion.

The over-all results of hyperparathyroidism, therefore, include hypercalcemia, hypophosphatemia, hypercalcinuria, hyperphosphaturia, and demineralization of the skeleton. The serum alkaline phosphatase may be normal or increased. The augmented quantities of calcium and phosphate in the urine favor the development of nephrolithiasis.

When, on the other hand, there is deficiency of the parathyroid hormone, the rate of renal phosphate excretion tends to decline, the blood inorganic phosphate rises, and a fall in the concentration of ionized calcium in the plasma occurs. When this process is sufficiently marked, tetany may occur as the result of the calcium-ion deficit.

Aside from its effects on calcium absorption and phosphate excretion, there is some evidence that the parathyroid hormone may have a third action—namely, a direct effect on bones, in tending to release phosphate and calcium into the plasma. The evidence for this view is the fact that in nephrectomized animals the hormone causes a rise in the plasma calcium and phosphate concentration. Whether this effect is, in fact, to be attributed to increased absorption of calcium and, secondly, of phosphate, from the gastrointestinal tract, or to withdrawal of these elements from the bones, does not seem to be entirely clear at present.

Whenever, for any reason, there is a decline in the level of ionized calcium in the plasma, the parathyroid glands are stimulated and the subsequent increase in their activity tends to restore the level of ionized calcium.

**Steroid Hormones in Relation to Calcium and Phosphorus.** The internal secretions of the ovaries, testes, and adrenal glands have important effects on calcium and phosphorus metabolism. These several hormones do not, as in the case of vitamin D and the parathyroid hormones, appear to affect the level of calcium and phosphorus of the plasma directly, but indirectly by altering the quantity of bone matrix. The estrogens and

androgens both appear to stimulate the formation of bone matrix, and this, in turn, leads to rapid deposition of calcium and phosphorus in the bones. This process appears to be of fundamental importance in relation to the rapid rate of skeletal growth which occurs at the onset of puberty in both sexes. The reverse process is apparently concerned in the demineralization of bone, which occurs in the postmenopausal state in women, and in elderly subjects of both sexes.

The adrenal cortex appears to have the opposite effect upon the bone matrix from that induced by the sex glands, since it stimulates the rate of formation of glucose from amino acids. Such a diversion of amino acids toward catabolic rather than structural utilization tends to inhibit the laying down of bone matrix, which is composed mainly of protein; and, secondarily, to inhibit the rate of bone mineralization. In this regard it should be remembered that bone can no longer be thought of as a relatively stable tissue. The isotope studies of recent years indicate that bone is continually being produced, and that this process in the adult is normally balanced by a corresponding rate of absorption of bone. Hence, any mechanism which diminishes the rate of formation of bone matrix, or the rate of mineralization of preformed matrix, will have the same effect as if there were either an increased absorption of matrix or a loss of calcium and phosphorus from the preformed matrix.

**The Kidney in Relation to Calcium and Phosphorus.** Normally, the urine is poor in calcium but rich in phosphorus. Since the plasma is poor in both of these substances, it is evident that phosphorus has the higher concentration ratio, and hence that renal excretory failure will tend to cause retention of phosphorus but not of calcium. Actually, in uremic states, the retention of phosphate leads to diminished ionization of calcium, and hence to calcium-ion deficit. Such a deficiency plays a role in the causation of twichings, convulsions, and other manifestations of increased neuromuscular irritability so frequently observed in the uremic states.

Patients with chronic uremia and long-standing calcium-ion deficiency frequently develop a secondary, compensatory hyperplasia of the parathyroid gland. This is commonly spoken of as renal, or secondary, hyperparathyroidism. As the result of this hyperparathyroid hyperplasia, and also of the chronic acidosis which accom-

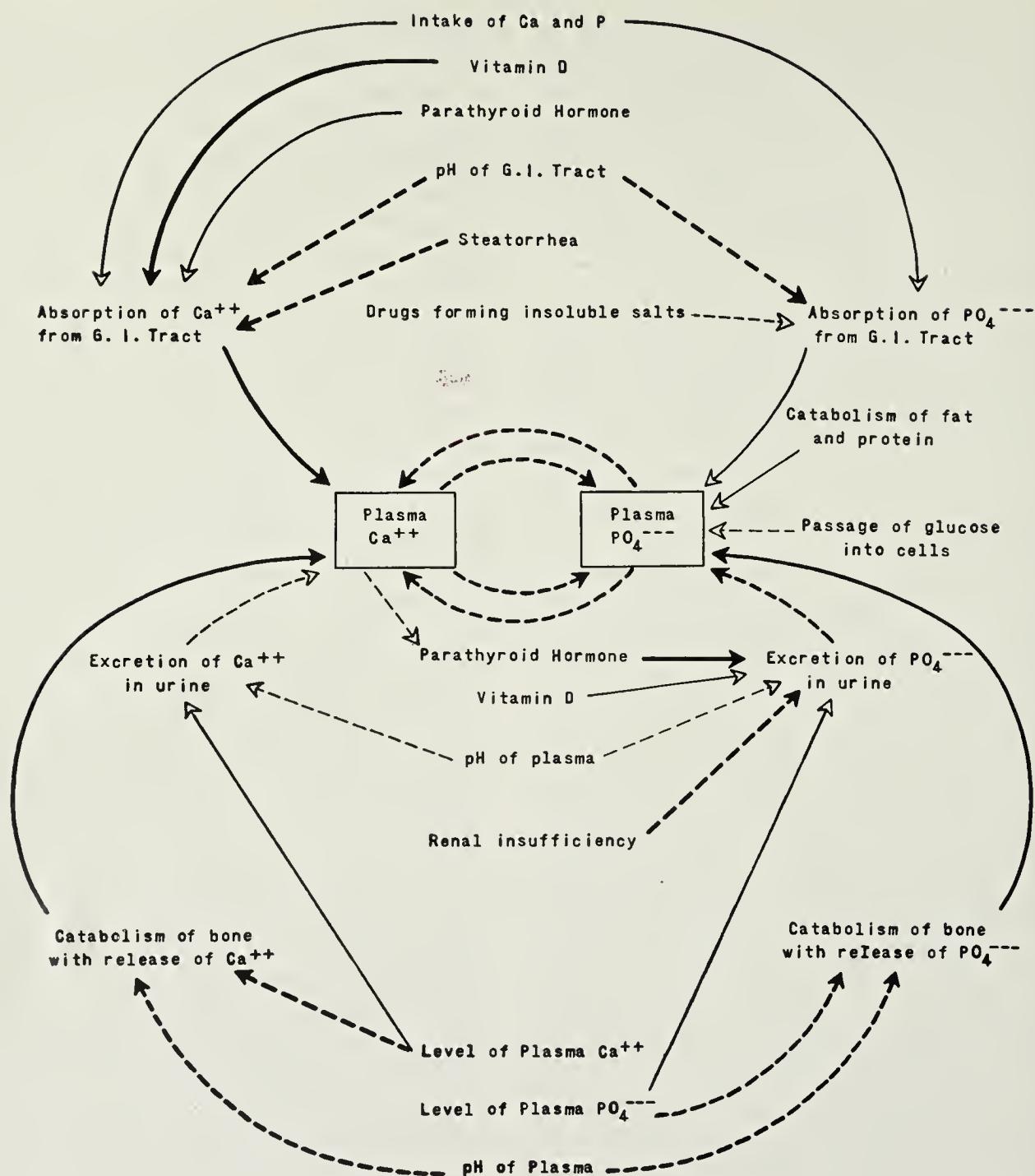


FIG. 34. Diagram of chief factors affecting the plasma levels of ionized calcium ( $\text{Ca}^{++}$ ) and inorganic phosphate ( $\text{PO}_4^{--}$ ).

The heavy arrows indicate that the factor concerned is of especial importance. The solid arrows ( $\longrightarrow$ ) indicate that the factor and its effect vary directly; the broken arrows ( $\dashrightarrow$ ) indicate that the factor concerned and its effect vary inversely. For example, increased intake of vitamin D tends to cause increased calcium absorption, but increased steatorrhea tends to cause decreased calcium absorption.

Note especially that: (1) Blood  $\text{Ca}^{++}$  and  $\text{PO}_4^{--}$  tend to vary inversely, an increase in either tending to decrease the other, and vice versa. (2) Decline in plasma  $\text{Ca}^{++}$  tends to increase the activity of the parathyroid glands, leading to increased excretion of  $\text{PO}_4^{--}$ , decrease in plasma  $\text{PO}_4^{--}$ , and rise in plasma  $\text{Ca}^{++}$ . (3) The effects of vitamin D and of parathyroid hormone are similar qualitatively, but dissimilar quantitatively; the former tending predominantly to increase absorption of  $\text{Ca}^{++}$ , the latter to increase excretion of  $\text{PO}_4^{--}$ . (4) The factors affecting absorption tend to affect  $\text{Ca}^{++}$  primarily, the effects on  $\text{PO}_4^{--}$  being secondary; while those affecting renal excretion act mainly on  $\text{PO}_4^{--}$ . (The ions indicated as  $\text{PO}_4^{--}$  are actually a mixture of monobasic and dibasic phosphate ions.)

Table 32

## SERUM LEVELS OF CALCIUM AND PHOSPHORUS IN RELATION TO COMMON DISORDERS OF BONE

	Total Serum Calcium	Serum $Ca^{++}$	Serum $PO_4^{--}$	Serum Alkaline Phosphatase
Hyperparathyroidism . . . . .	+	+	-	+
Hypoparathyroidism . . . . .	-	-	+	Normal
Rickets . . . . .	Normal or -	Normal or (- with tetany)	-	+
Renal rickets . . . . .	-	-	+	Normal or rarely +
Osteomalacia . . . . .	Normal or -	Normal or -	Normal or +	Normal or +
Senile osteoporosis . . . . .	Normal	Normal	Normal	Normal or +
Paget's disease . . . . .	Normal	Normal	Normal	+
Calcinosis universalis and circumscripta . . . . .	Normal	Normal	Normal	Normal
Marble bone disease . . . . .	Normal	Normal	Normal	Normal or +
Metastatic carcinoma of bone . . . . .	Normal	Normal	Normal	Normal or +
Osteogenic sarcoma . . . . .	Normal	Normal	Normal	Normal or +
Multiple myeloma . . . . .	Normal or +	Normal	Normal	Normal or +
Fractures of bones . . . . .	Normal or +	Normal	Normal	+

panies states of renal insufficiency, there is withdrawal of calcium and of phosphorus from the bones, leading to the condition commonly spoken of as *renal rickets*.

Under exceptional conditions, the kidneys may retain chloride ions excessively. The state of hyperchloremia so induced, with the consequent acidosis, leads to increased excretion of calcium and withdrawal of calcium from the bones, and may be followed by renal stone formation (nephrolithiasis) or by calcification of the renal parenchyma (nephrocalcinosis).

A different type of disturbance in calcium metabolism resulting from renal disease is that which is seen in the rare disorder (*Fanconi syndrome*) in which long-standing renal glycosuria produces ketosis, and the resulting state of acidosis leads to withdrawal of calcium from bones and increased excretion of calcium into the urine.

**Factors Affecting Plasma Level of Calcium and Phosphorus.** The chief mechanisms have already been mentioned and no detailed comment is necessary, since they are summarized in the accompanying diagram (fig. 34).

**Serum Alkaline Phosphatase.** The intimate process by which the mineral substance of bone is deposited is believed to involve the enzymic hydrolysis of phosphate esters, so that local excessive concentrations of inorganic phosphate are provided to favor the precipitation of the mineral in the bone matrix. The phosphatase enzyme or enzymes concerned are characterized by having pH optima on the alkaline side of neutrality (pH 9.0 to 9.6), and are found in greatest quantity

in osteoblastic cells. Small amounts of the enzyme apparently gain entry to the vascular system and are responsible for the normal slight alkaline phosphatase activity of serum (2 to 4 Bodansky units in the adult; 5 to 14 Bodansky units in infants and children). The circulating enzyme is excreted at least in part via the bile, and retention is at least one of the factors responsible for the marked increase in serum alkaline phosphatase associated with obstruction of bile ducts, or the lesser degrees of increase observed in parenchymatous liver disease.

~~Increases in serum phosphatase activity~~ of moderate to marked degree are generally observed in those disorders associated with ~~increased osteoblastic activity~~—e.g., Paget's disease. On the other hand, lesions associated with ~~increased osteoclastic activity are much less apt to be accompanied by a significant rise~~. Thus in patients with hyperparathyroidism the serum alkaline phosphatase may be normal or only moderately increased. The direction of alteration of serum alkaline phosphatase in some of the disorders involving bone is given in table 32.

The discussion above refers only to alkaline phosphatase. ~~Serum acid phosphatase~~, an entirely different enzyme, having a pH optimum of about 4.8, is elevated in patients with carcinoma of the prostate. Such an elevation of the acid phosphatase is, therefore, of specific diagnostic import. Fortunately, the pH optima of alkaline and acid phosphatases are sufficiently different so that neither exhibits appreciable activity at the pH optimum of the other. This permits the

rather accurate laboratory determination of one in the presence of the other without significant overlapping, providing proper care is employed in the control of the pH factor.

### COMMON DISORDERS OF BONE IN RELATION TO CALCIUM AND PHOSPHORUS

#### 1. Deficiency of Bone Matrix (Osteoporosis).

Three general causes may be considered:

a. Bone matrix becomes deficient when bones are not used to normal degree. Hence such a mechanism is important in patients who are rigidly confined to bed for a long time, for any reason; and under such conditions all of the bones tend to become demineralized. The same mechanism is responsible for local demineralization in bones which are immobilized in the course of orthopedic management.

b. Alterations in steroid metabolism. Deficiencies of estrogens or androgens are concerned in the demineralization which occurs in women following the menopause, and in both sexes at advanced ages. Likewise, and for the reasons which have been mentioned, excessive activity of the adrenal cortex (Cushing's syndrome, adrenal cortical tumors) tends to lead to demineralization.

c. Disorders of protein metabolism. Such a mechanism is apparently responsible for the demineralization occurring in advanced states of malnutrition, the protein matrix of the bone, like other body protein, being utilized for energy.

**2. Defective Deposition of Phosphorus and Calcium in Bones (Osteomalacia).** Aside from those disorders already mentioned, in which the primary deficiency appears to be in the matrix, there is a group of disorders in which the normal matrix cannot become normally mineralized. The most important of such disorders are the following:

a. Rickets due to defective absorption of calcium, consequent to vitamin D deficiency in children.

b. Osteomalacia, a disorder similar to rickets but occurring in adults and due to deficiency of vitamin D as the result either of inadequate intake or, more commonly, of defective absorption of calcium because of steatorrhea. (Certain investigators reserve the term "osteomalacia" for deficient mineralization specifically due to vitamin D deficiency, while others use the term to

designate all of the disorders in which there is defective deposition of calcium and phosphate in the presence of normal matrix.)

c. Excessive excretion of calcium in the urine and consequent deviation of calcium from bones as the result of renal disease. Such conditions have already been discussed.

**3. Increased Loss of Calcium and Phosphorus from Bones.** Hyperparathyroidism constitutes the classic example; and, as shown in table 32, somewhat similar mechanisms are operative in extensive neoplastic disease of bones and in Paget's disease.

### CERTAIN CONSIDERATIONS OF NEPHROLITHIASIS

The formation of kidney stones tends to be favored by conditions which cause increased renal calcium excretion. The most important of such conditions are chronic acidosis from any cause, and hyperparathyroidism. Stone formation is likewise favored by those conditions which tend to cause precipitation of insoluble calcium salts in the urinary tract. Of such conditions, the most important are local stasis and infection. Infection with urea-splitting organisms may cause excessive production of ammonia from urea, with consequent increase in alkalinity, and since phosphate salts of calcium are less soluble in alkaline than in acid solution, they tend to precipitate. It will be apparent that the therapeutic use of alkali salts has a paradoxical effect in relation to stone formation. On the one hand, the administration of moderate amounts of alkali tends to decrease the excretion of calcium in urine, while, on the other hand, the alkaline urine induced by such therapy favors the precipitation of calcium salts. It appears that when acidosis exists alkaline therapy tends to prevent stone formation, while in the absence of acidosis such therapy may have the reverse effect. Such considerations apply, of course, only to calcium stones. Other aspects of nephrolithiasis are considered in Chapter 19.

### MAGNESIUM

Normally, a small quantity of magnesium amounting to 1 to 3 mg. % is present in the plasma of blood, and slightly larger quantities are to be found in the erythrocytes. The concentration in interstitial fluid is somewhat lower

than that of plasma, but in intracellular fluid it constitutes some 15 to 20 per cent of the total alkali cation. The functions of magnesium are not well understood, although it is now demonstrated that certain enzymic catalytic systems are dependent upon the presence of magnesium ion. It has been seen that moderate changes in concentration of the other cations in extracellular fluid are attended by marked changes in functions of various kinds. Similar fluctuations in magnesium concentration do not seem to be attended by functional changes, and, in addition, magnesium concentrations have not been shown to exhibit wide variations in conjunction with disorders of acid-base and fluid balance.

Magnesium deficiency has been induced experimentally, and the syndrome manifested includes circulatory disturbances, increased irritability, convulsions, and, finally, death. Deficiency syndromes have also been observed in cattle fed certain diets in which the plasma magnesium concentration has been shown to be markedly reduced. In the human, however, magnesium deficiency has not as yet been demonstrated. This essential mineral is present in sufficient quantities in such a variety of foods that almost all natural diets are adequate in respect to it.

Magnesium excess may be produced experimentally by the injection of magnesium salts. Moderate increases of magnesium-ion concentration in plasma (e.g., 5 to 10 mg. %) are soporific, and with further increases (e.g., 20 to 40 mg. %) profound coma supervenes, death occurring from respiratory failure.

In man magnesium excess is occasionally produced as a result of the administration of excessive amounts of magnesium salts, parenterally, or as the result of employment of such salts as purges in patients with markedly impaired renal function. The symptoms resulting are those observed experimentally—i.e., apathy merging into stupor and coma.

Although the dietary intake of magnesium may vary tremendously, increases in its concen-

tration in body fluids normally do not occur, as it is readily eliminated in the urine.

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## Section 4—Intermediary Metabolism

# 30

## Principal Pathways of Intermediary Metabolism

M. F. Mason and Kendall Emerson, Jr.

### Certain Present-Day Concepts of Intermediary Metabolism

Role of Vitamins and Hormones in Metabolism

Breakdown of Carbohydrate

Entry of Protein into the Metabolic Pool

Entry of Fat into the Metabolic Pool

Aerobic Oxidation

Certain Aspects of the Role of the Liver in Metabolism

### Mechanisms of Certain Disorders of Intermediary Metabolism

Hyperglycemia and Diabetes

Ketosis

Hypoglycemia

The Fatty Liver

### CERTAIN PRESENT-DAY CONCEPTS OF INTERMEDIARY METABOLISM

The term "intermediary metabolism" refers to that phase of biologic science which deals with the chemical transformation of foodstuffs in the body.

The essential exogenous foodstuffs consist of minerals, certain amino acids and fatty acids, and some other organic structures, many of which are now recognized as vitamins, and which cannot be synthesized within the body. In spite of the fact that it is not an essential foodstuff (i.e., not necessary in the diet to sustain life), the larger part of the diet of most individuals consists of carbohydrates, because of its availability and inexpensiveness as compared to fat and protein.

Studies in recent years, particularly those which have employed isotopes as tracers, have shown that the previously accepted concepts of the relative independence of the various foodstuffs and the sharp separation of exogenous and endogenous metabolism are no longer tenable. Instead, it has been shown that the derivatives of ingested protein, fat, and carbohydrate constitute a common metabolic pool which is in dynamic equilibrium with the various tissue structures. The conversion of one foodstuff to another may take place rapidly within this pool, and many of the reactions concerned occur in the liver. It is likely that there is a common final

metabolic pathway in most tissues, so that the terminal chemical reactions of disintegration of carbohydrate, fat, and protein are identical, involving the disposal of a limited number of kinds of molecules which may have originated from any of these three sources. The essential purpose served by such disintegration is to provide energy for support of anabolic processes and the performance of mechanical work. Thus the energy is employed to drive those reactions in the body which are endergonic; i.e., reactions which cannot proceed spontaneously, and which require an input of energy. In the resting organism, which is neither gaining nor losing weight, all of this energy ultimately is dissipated as heat. Inasmuch as disease is often, if not always, due to or accompanied by dislocations in rate or integration of the reactions of intermediary metabolism, it is necessary to have a general understanding of the processes involved in the release of energy from food. *That such an understanding is not only of theoretic interest but of great practical importance becomes clear when it is realized that such diverse disorders as diabetes mellitus, beriberi, pellagra, cyanide intoxication, and probably diphtheria, are all dependent upon disturbances of known intermediary reactions.* It seems certain that many other clinical conditions will soon be correlated with such disturbances.

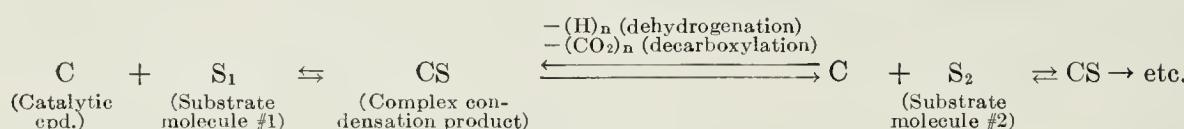
Study of the nature of catabolism (i.e., the progressive breakdown) of foodstuffs in the body cells has revealed certain broad principles, among which the following are some of the most important.

1. Foodstuff substrates (i.e., the chemical substances altered by enzymes) are oxidized by removal of hydrogen atoms, or addition of water together with removal of hydrogen atoms, the latter ultimately being employed to reduce molecular oxygen to form water.

2. Carbon dioxide arises by virtue of CO<sub>2</sub> split-

ting out of the carboxyl groups of organic acids (decarboxylation).

3. Carbohydrate, fat, and protein are converted by enzymatic action into a limited number of smaller substrate molecules which are not then completely oxidized as such, but rather appear to form complex molecules by condensation with certain catalytic compounds. Hydrogen atoms and  $\text{CO}_2$  are removed from the complex by a series of reactions which releases the original catalytic compound, enabling it thereby to condense with another substrate molecule. The net effect, which permits the continuous disposal of these substrate molecules, may be represented as follows:



4. Oxygen does not appear to be directly involved in the various reactions in which hydrogen and  $\text{CO}_2$  are removed from substrates. It is largely employed only in the terminal reaction of metabolism, in which it is reduced by hydrogen to form water.

5. Most, if not all, of the reactions by which foodstuffs are degraded are catalyzed by enzymes and/or catalytic compounds which act as hydrogen (electron) transfer agents (see below). Many of these reactions are reversible and the same enzymes may catabolize under one set of conditions and synthesize under another.

6. A considerable fraction of the chemical energy obtained from these reactions is employed in the phosphorylation of a variety of compounds. In some instances this appears to be a necessary preliminary to further degradation, or to transformation or translocation of the molecule involved. In others, it establishes a so-called "energy-rich phosphate bond" which, upon hydrolysis, like the combustion of gunpowder, suddenly releases a large amount of energy which may be employed to drive endergonic reactions—i.e., reactions which require an input of energy in order to proceed. Examples of this are the establishment by phosphorylation of some other energy-rich bond itself, or synthesis of complex molecules. It should be pointed out that only a few of the phosphate ester linkages formed in metabolic reactions are "energy-rich." The remainder yield only moderate amounts of energy

upon hydrolysis, and do not appear to be employed in driving other reactions.

### ROLE OF VITAMINS AND HORMONES IN METABOLISM

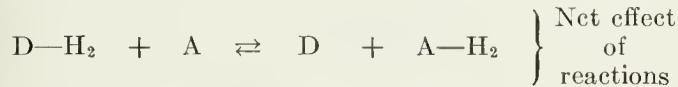
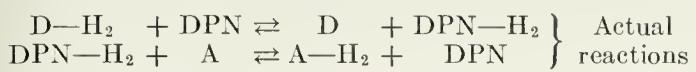
In the course of the metabolic breakdown of foodstuffs, vital roles are played by enzymes, vitamins, and hormones. Many enzymes are composed of proteins combined with certain simpler substances termed prosthetic groups, which together form the complete catalytic enzyme system. Some of these prosthetic groups are vitamins of the B group, and are known as coenzymes. Iron-porphyrin compounds constitute the prosthetic groups of certain important oxidative en-

zyme proteins. In addition, traces of certain metals such as magnesium, manganese, calcium, cobalt, or iron; anions such as chloride; or, occasionally, organic structures functioning as "activators" or phosphate transfer agents (e.g., adenylic acid) may be necessary to permit the catalytic action. The role of hormones is not yet so clearly defined as that of vitamins, yet there is increasing evidence that in many instances these substances, too, participate in the facilitation or inhibition of enzymatically catalyzed reactions.

Thus diphosphothiamine (cocarboxylase) is the coenzyme in the system which catalyzes reactions whereby carbon dioxide is evolved from the carboxyl ( $-\text{COOH}$ ) groups of certain acids, such reactions being quantitatively the only important sources of  $\text{CO}_2$  of metabolic origin. Most of the carbon dioxide so formed is excreted, but recent evidence indicates that some of it may be immediately employed for resynthesis of a variety of complex organic molecules, including glycogen. Diphosphothiamine is concerned in such reactions which reutilize carbon dioxide.

Nicotinic acid amide, as a component of the di- and triphosphopyridine nucleotides (designated as DPN and TPN, or coenzymes I and II, respectively), enters into a number of reactions, the feature of which is the transfer of hydrogen atoms or electrons from one compound to another, by virtue of the reversible oxidation and reduction of the nucleotide. This results in the

oxidation by removal of hydrogen atoms from one substance (the donor) and the reduction of another (the acceptor), and may be represented schematically as follows:



( $\text{D}-\text{H}_2$  = donor molecule;  $\text{D}$  = oxidized donor;  $\text{A}$  = acceptor molecule;  $\text{A}-\text{H}_2$  = reduced acceptor molecule.)

In certain instances only electrons are actually transferred, the hydrogen atoms donating these becoming hydrogen ions in the aqueous environment ( $2\text{H} = 2\text{H}^+ + 2(\text{e})$ ).

Riboflavin as a component of the flavine nucleotides is the prosthetic group of a number of enzyme proteins, and as such is an electron and hydrogen transfer agent. It is quite probable that a number of other members of the B complex have similar functions. Thus it appears that Vitamin B<sub>6</sub> (pyridoxine, pyridoxal, pyridoxamine) is the prosthetic group of enzymic proteins catalyzing transamination (i.e., the transfer of an amino group from one compound to another), and is also the cocarboxylase involved in the decarboxylation of certain amino acids. Pantothenic acid has been demonstrated to act as a coenzyme for acetylation reactions, and may have other functions.

Recent investigation suggests that one of the chief actions of insulin is that of releasing the physiologic inhibition of the enzyme hexokinase, imposed by the diabetogenic hormone of the anterior pituitary gland, and possibly reinforced by a factor present in adrenal cortical extract.<sup>1</sup> Hexokinase catalyzes the reaction whereby glucose is phosphorylated by adenosine triphosphate and adenosine diphosphate to become glucose-6-phosphate, a preliminary step necessary before glucose may be catabolized or converted to glycogen. It is likely that all hormones exert their

<sup>1</sup> At the present time (November 1949) these findings and their interpretation are subjects of some controversy. Because of numerous confirming reports, and because such a role of insulin in the intact organism affords a convenient working hypothesis for explanation of many of the features of the diabetic state, the assumption of this action of insulin is employed in the subsequent discussion with full realization that future investigation may either modify, contradict, or extend the concept. The possibility that insulin may have other important actions is clearly recognized.

effects by altering the rates of certain reactions, of which this is one of the early examples demonstrated. Some of the regulating effects of hormones on metabolism are discussed in more detail subsequently.

In some instances the consequences of deficiency (or excess) of individual hormones or vitamins are disorders clearly recognized clinically—e.g., diabetes, pellagra, and beriberi, due to lack of insulin, nicotinic acid, and thiamine, respectively. In other instances, the manifestations of deficiency are not yet recognized readily—e.g., pyridoxine deficiency.

### BREAKDOWN OF CARBOHYDRATE

Because the breakdown of carbohydrate illustrates some of the principles mentioned, and since, in addition, the latter stages appear to proceed by a pathway employed also in both fat and protein catabolism, some of the processes involved may be sketched briefly. The metabolism of carbohydrate is not more important than that of protein and fat, but is emphasized here because it has been clarified during recent years, and its discussion will better serve the purpose of illustrating the general principles of intermediary metabolism. The main features of carbohydrate metabolism in relation to those of fat and protein are indicated in figure 35.

The catabolism of carbohydrate may be divided conveniently into several stages, including (1) the formation of hexose phosphate and glycogen; (2) anaerobic glycolysis; (3) aerobic oxidation, and (4) disposal of the hydrogen atoms removed.<sup>2</sup> The two latter stages represent the common final pathway for fat and protein, as well as for carbohydrate.

**1. Entry into the Metabolic Pool as Hexose Phosphate.** Glucose in body fluids is not directly attacked by cells, but is first converted to glucose-6-phosphate by the transfer of phosphate from adenosine triphosphate (ATP) or adenosine diphosphate (ADP), the latter substances being subsequently reconstituted by energy-yielding reactions in which they act as phosphate acceptors. Inasmuch as this reaction must occur before

<sup>2</sup> The distinction between anaerobic glycolysis and “aerobic oxidation” is merely one of tradition and convenience. Oxygen, as such, is employed only in the terminal disposal of hydrogen ions and electrons. (See later discussion of aerobic oxidation.)

glucose may be either converted to glycogen or catabolized in the liver or muscles, this is obviously a process of great significance. It should be pointed out, however, that our recognition of the importance of this reaction arises only from the

tion of carbohydrate residues. Extracellular fluid is, in part, the reservoir of the water and electrolytes required. Thus proper hydration—i.e., normal volume and composition of extracellular fluid—is necessary if utilization of carbohydrate

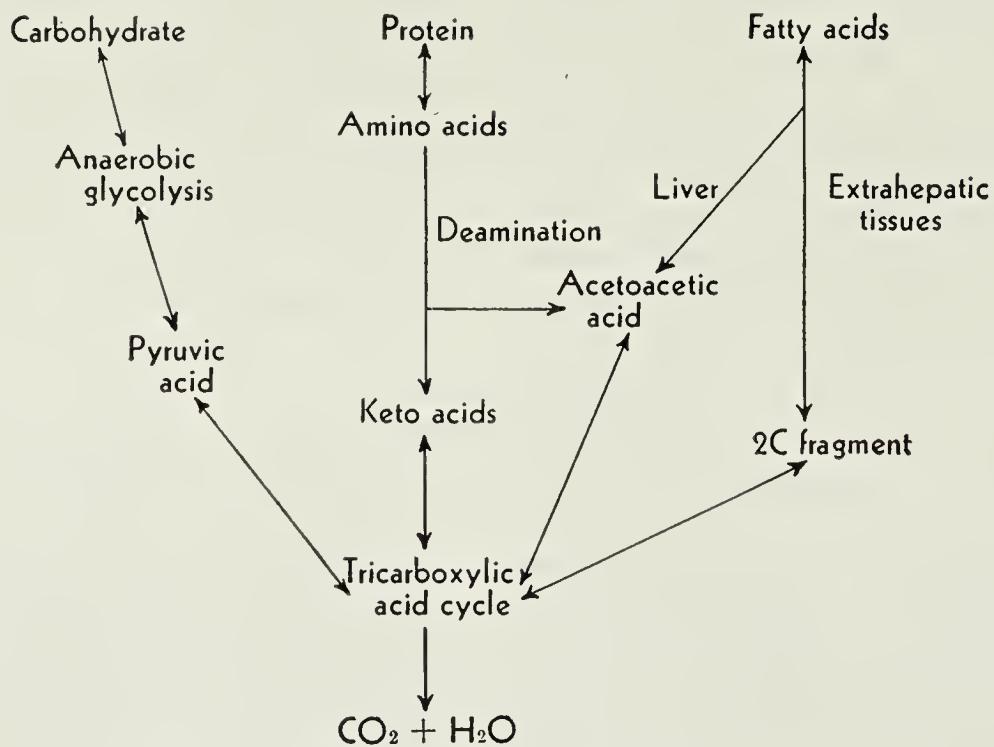


FIG. 35. The schematic representation above deals only with the chief features of main catabolic pathways. Alternate pathways, pathways of synthesis, and mechanisms of interconversion, etc., are omitted.

fact that the consequences of marked alterations in its rate are so evident (diabetes mellitus, hypoglycemia). It is probable that other reactions, which at the moment appear more or less incidental, will assume similar importance as the factors which govern their rates and the results of their distortion are defined. Thus recent evidence suggests that increased hepatic phosphatase activity may be an important operative factor in the diabetic state.

As glucose enters the metabolic pool the accumulation of phosphorylated derivatives leads to a marked decline of the inorganic phosphate content of body fluids. This later returns to normal as glycogen is formed, or as the phosphorylated derivatives are disposed of, oxidatively. Less in degree, but more prolonged, is the decline in potassium content of extracellular fluid. This is accounted for by fluid of intracellular electrolyte composition accompanying glycogen deposited in liver and muscles, or new proteins whose formation involved amination and utiliza-

is to proceed normally. In the presence of deficiency in sodium chloride and water ("dehydration") the insulin required to facilitate glycogen utilization may be greatly increased, and severe losses of fixed base are almost always accompanied by decreased carbohydrate utilization with resultant ketosis (see below).

The conversion of glucose to glucose-6-phosphate may be reversed in the liver by a specific phosphatase, but this does not occur in muscle where this enzyme is lacking. Hence liver glycogen may directly serve as a source of blood sugar, but muscle glycogen cannot. Glucose-6-phosphate may be converted to glycogen or degraded to pyruvic acid. The conversion to glycogen involves two reversible reactions, providing a means whereby stored glycogen may revert again to glucose-6-phosphate whenever the rate of phosphorylation of blood sugar is slower than the rate at which the tissue concerned is utilizing carbohydrate. Figure 36 illustrates the main reactions and enzymes involved.

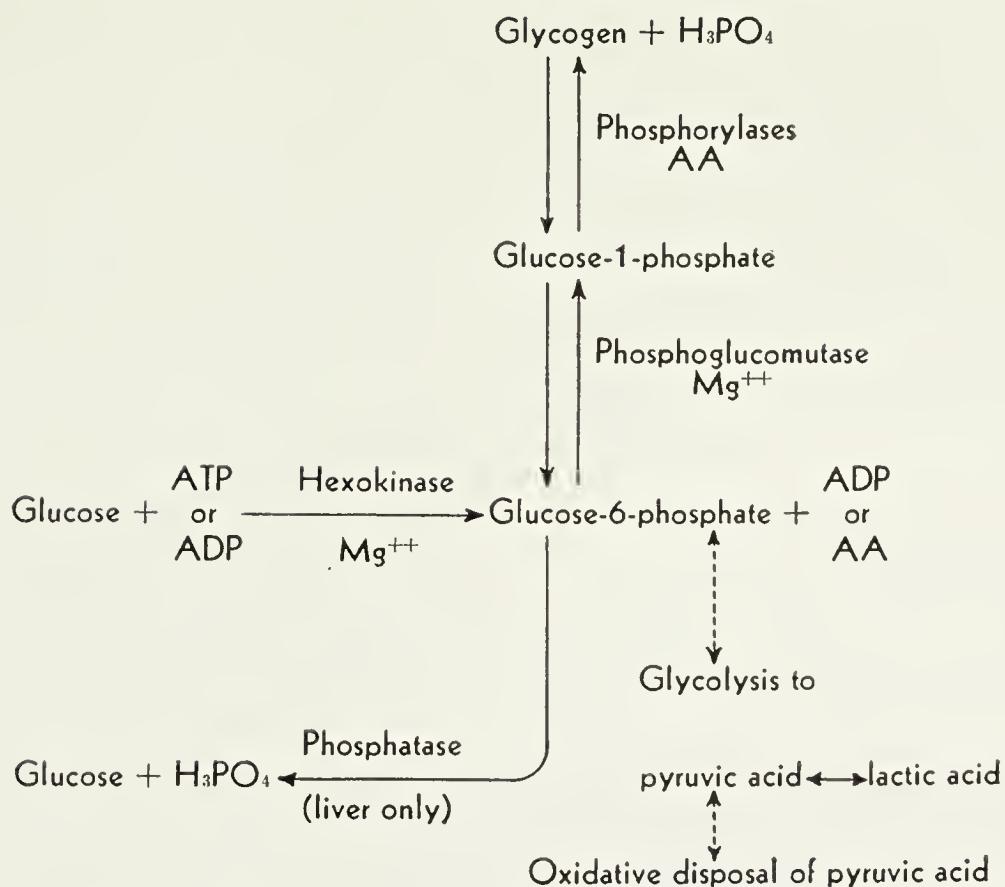


FIG. 36. The entry of glucose into the metabolic pool, as illustrated here, shows three pathways for disposal of the glucose-6-phosphate formed. (AA) Adenylic acid; (ADP) adenosine diphosphate; (ATP) adenosine triphosphate. Solid arrows indicate a single transformation; broken arrows designate several intermediate reactions not shown in diagram.

**2. Anaerobic Glycolysis.** The first phase of catabolism of glucose-6-phosphate consists of the formation of an equilibrium mixture of glucose and fructose-6-phosphate. The latter is then phosphorylated at the 1-position and undergoes a series of anaerobic reactions whereby it is split into two 3-carbon phosphorylated fragments with eventual formation of pyruvic acid and release of the two phosphate radicals. The net effect of these reactions is to supply energy which is utilized in part to restore the two phosphate radicals to their position in adenosine triphosphate from where they were originally derived, and thus to enable the process to be repeated continuously. In the presence of a sufficient oxygen tension, the pyruvic acid is oxidatively removed (see below), but if the oxygen tension is inadequate the pyruvic acid is reduced to lactic acid (fig. 37). Thus in normal resting muscle there is only a small amount of lactate formed, this presumably due to minimal transient anaerobiosis occurring intermittently in portions of the capillary bed. In violent exercise, however, the oxygen tension may so decline that large amounts of lactate are formed. Some of this lactate may be locally reoxidized to pyruvate when the oxy-

gen tension subsequently becomes adequate again, but the larger fraction diffuses into the blood, and is eventually converted to glycogen in the liver.

This series of reactions, by which hexose phosphate becomes pyruvic acid, is termed the "anaerobic glycolytic cycle." All of the reactions of the cycle are reversible. Its importance in the intermediate metabolism of carbohydrate as well as fat has recently been emphasized by Stetten's demonstration that in normal animals approximately 95 per cent of ingested carbohydrate goes through this cycle before being completely oxidized or converted to fat or glycogen, while only about 5 per cent is converted directly to glycogen.

#### ENTRY OF PROTEIN INTO THE METABOLIC POOL

It should be noted in figure 37 that in the course of the disposal of carbohydrate, pyruvic acid and other keto acids are formed. These may be derived not only from carbohydrate but also from protein via amino acids or from fat. It is chiefly as keto acids that amino acid derivatives appear to enter the final common metabolic pathway.

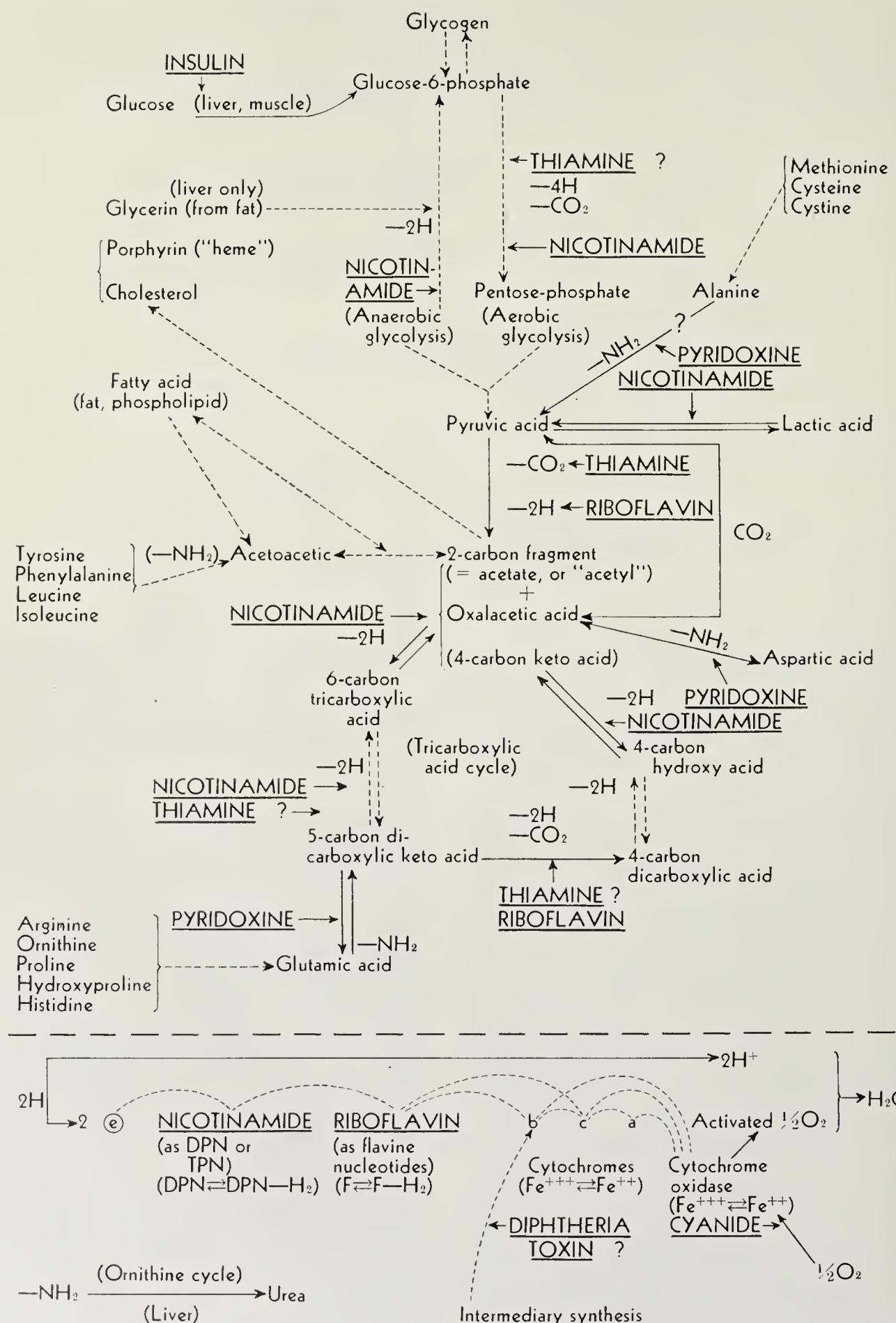


FIG. 37. This figure is a schematic representation of some of the chief features of intermediary metabolism. Its (Continued on facing page.)

In the breakdown of protein the chief processes concerned are deamination of the free amino acids in the liver, with conversion of the amino group to urea or ammonia, and utilization of the resulting keto acid.<sup>3</sup> The reservoir of free amino acids ("metabolic pool") is maintained by amino acids obtained from exogenous protein, or endogenously by the continuous exchange taking place between structural protein and free amino acids ("the dynamic equilibrium").

It appears that the carbohydrate-regulating hormones derived from the adrenal cortex and the adrenocorticotropic hormone of the pituitary gland act in such a way as to favor the catabolism of proteins into amino acids (clinical evidence suggests that the thyroid hormone has a similar effect). On the other hand, testosterone and the androgenic hormones of the adrenal cortex appear to facilitate protein synthesis. Insulin tends to inhibit protein breakdown, but this effect may be indirect in that the acceleration of the rate of phosphorylation of glucose makes the carbohydrate derivatives more available for metabolism, and these substances, by competition for enzyme systems, tend to inhibit the breakdown of protein. When body protein is metabolized, the excretion of water, electrolytes such as potassium and phosphorus, and nitrogen in the urine are correspondingly increased, as these are derived from the tissue so utilized. Similar losses of these substances occur if gluconeogen-

esis from body protein is accelerated. On the other hand, the urinary outputs are diminished if body protein is being deposited.

In the breakdown of nucleoprotein, one of the final end products derived from the purine moiety of the original substance is uric acid. This is formed as a result of the action of a specific enzyme, xanthine oxidase. The recently discovered vitamin B<sub>12</sub>, which has been shown to have remarkable curative powers in pernicious anemia, is thought to be one of the regulators of nucleoprotein metabolism.

#### ENTRY OF FAT INTO THE METABOLIC POOL

The larger fraction of fatty acids normally metabolized is directly oxidized in the peripheral tissues, apparently without the intermediate formation of 4-carbon ketones. The remaining smaller portion of the fatty acids derived from neutral fat, phospholipid, or cholesterol ester, whether arising from the food or from the body stores, is broken down in the liver by means of beta-oxidation (i.e., the progressive splitting off of two carbon atom fragments proceeding from the carboxyl end of the molecule) with reconstitution of the 2-carbon fragments to form acetoacetic acid. From this, beta-hydroxybutyric acid is readily formed by reduction, or acetone is derived by decarboxylation. Ordinarily, these ketones are carried to the peripheral tissues and oxidized as rapidly as they are formed, but when the rate of formation in the liver becomes faster than the

<sup>3</sup> The keto acid may be either reaminated or oxidatively utilized.

FIG. 37—(Continued)

purpose is to illustrate the importance in clinical medicine of fundamental biochemical principles. Hence sites of action of certain vitamins, hormones, and toxins are indicated.

Reactions indicated by solid arrows in the upper portion of the diagram are individual reactions; those indicated by dotted arrows represent conversions involving more than one reaction. CO<sub>2</sub> and hydrogen arising by decarboxylation and dehydrogenation are indicated. The site of operation of insulin and some of the vitamins is indicated by underlining. (There is evidence—less well established at the present time—that several other members of the B complex are concerned in the reactions shown.)

The lower part of the diagram indicates the means of conversion of the hydrogen atoms to water, by combination with oxygen. The hydrogen atoms yield hydrogen ions and electrons. The latter are transferred from the primary acceptor (nicotinamide [as DPN or TPN] or riboflavin [as a dinucleotide], underscored in upper diagram) through the series shown in the lower diagram, eventually to oxygen. The combination of the thus "activated" oxygen and hydrogen ions forms water. The electron transfers are indicated by curved dotted lines. Note that by-passing may occur in this "bucket brigade." The sites of action of cyanide and, possibly, of diphtheria toxin are shown (under-scored). The conversion of amino groups to urea is also indicated.

Note that carbohydrate is degraded to pyruvic acid, which is then decarboxylated and condensed with a catalytic substance (oxalacetic acid) to form a tricarboxylic acid. The removal of hydrogen and CO<sub>2</sub> from this regenerates the oxalacetic acid (tricarboxylic acid cycle, final common metabolic path). The site of entry of some of the amino acids (from protein metabolism) into the system at the pyruvic acid stage, and subsequently, is shown; likewise, the entry of fatty acids as two-carbon fragments directly or via acetoacetic acid. The cyclic nature of the system disposing of pyruvate, the reversibility of the reactions of anaerobic glycolysis, and many others, and various transamination reactions (not shown) permit rapid and complex interconversion of the primary foodstuffs, carbohydrate, fat, and protein (amino acids). (DPN) Diphosphopyridine nucleotide; (e) electron; (F) flavine nucleotide; (TPN) triphosphopyridine nucleotide.

rate at which the peripheral tissues can dispose of them, they accumulate in the blood, and ketosis develops which can be detected clinically. Ketosis, then, occurs when fat metabolism in the liver becomes accelerated beyond certain limits, this usually being the case when the glycogen stores of the liver are depleted. The final disposal of both ketones and peripherally oxidized fatty acids appears to occur by entry into the final common metabolic path. The breakdown of fat into ketone acids seems to be facilitated by some of the hormones of the adrenal and the anterior pituitary glands, while the process is inhibited in some manner by insulin. As long as there is sufficient carbohydrate and insulin to make the carbohydrate available for oxidation and to maintain liver glycogen stores, ketosis does not occur, but in the absence of insulin and consequent decline in the rate of phosphorylation of glucose, the liver glycogen stores decline and the rate of fat and protein metabolism in the liver increases. It has been suggested that a reduction in available pyruvate due to decreased carbohydrate breakdown restricts one of the normal pathways for 2-carbon fragments arising from fat (i.e., entry into the Krebs cycle). Consequently, a greater mass of 2-carbon fragments is subject to condensation into the 4-carbon ketones.

Not all of the products of protein and fat metabolism which enter the common metabolic pool are oxidized immediately. In the case of protein, it has been shown clearly that the derivatives may be converted into glucose, this process being known as gluconeogenesis. In addition, there is continuous exchange between free amino acids and those in tissue proteins, as well as interconversion of some amino acids to others by transfer of amino groups to keto acids (transamination). This free exchange is limited by the inability of the organism to form for itself certain amino acids which, therefore, must be obtained from exogenous sources. In the case of fat, there seems no reason for debate as to whether or not a similar production of glucose can occur, for much recent evidence suggests that such is the case. The question which remains unsettled is largely a matter of the magnitude which the process of gluconeogenesis from fat may attain. There is likewise much evidence to indicate that the excessive amount of glucose in the body fluids of diabetic patients, even when receiving a diet very low in carbohydrate, is the result not of deficient

utilization of glucose by the tissues, but of an excessively rapid gluconeogenesis from protein and possibly from fat which is accompanied by a decline in its rate of phosphorylation, the latter process only attaining a normal rate at high levels of blood sugar.

**Cholesterol.** The understanding of the intermediary metabolism of cholesterol is so limited at the present time that it is difficult or impossible to account for the increases or decreases in its concentration in body fluids which are observed in a variety of diseases. Likewise, the relationship of cholesterol metabolism to the tissue alterations observed in disorders such as atherosclerosis is not clear.

The cholesterol of blood consists of two fractions, free and esterified (with fatty acids) cholesterol which are present in both plasma and erythrocytes. In the plasma, cholesterol ester predominates; in the erythrocyte, most of the cholesterol is in the free form. The normal range of plasma cholesterol concentration in fasting subjects is rather wide, varying from about 150 mg. % to 250 mg. %, expressed as total cholesterol (= sum of free and ester cholesterol). The esterification other than that occurring during the absorption of exogenous cholesterol appears to take place largely in the liver, hence parenchymatous damage of this organ may be accompanied by a decline in the percentage of the plasma cholesterol which is in the ester form.

It is known that cholesterol may be both synthesized and destroyed in the mammalian body. Thus normal growth and development may occur upon a diet almost devoid of cholesterol. On the other hand, although large amounts of exogenous cholesterol may somewhat increase the body content of this sterol, only a fraction of such exogenous intake may be accounted for by this accumulation, and by excretion. A variety of evidence supports the contention that, normally, the intermediary destruction of cholesterol is nicely balanced with the intermediary synthesis, excretion, and absorption of exogenous sterol, so that the total body cholesterol and its body fluid concentrations remain little changed. It is not clear, however, whether the response to an increase in exogenous cholesterol is increased intermediary destruction or depressed intermediary synthesis, although the former seems most likely.

Isotopic studies have recently yielded the surprising finding that the intermediary synthesis of cholesterol is achieved with very small molecules as building stones. Of those studied it was found that acetic acid (acetate) could provide about half the carbon and hydrogen atoms required, these being distributed in all parts of the molecule. The origin of the remaining carbon and hydrogen is at present unknown. The various labeled substances other than acetate, which were shown to act as precursors of cholesterol, did so roughly in proportion to their ability to yield acetyl groups in the course of their metabolism, except in the case of alanine, an immediate pyruvate precursor, and thus, presumably, in the case of pyruvate itself and other immediate pyruvate precursors. This finding would seem to indicate that the 2-carbon fragment arising from the decarboxylation of pyruvic acid in carbohydrate metabolism is unlikely to be identical with 2-carbon fragment arising from fatty acid or ketone body oxidation, although these fragments, whether they arise from ketones, higher fatty acids, or acetic acid, are commonly referred to as "acetyl groups," as has been the case in this discussion (see above). The actual transient structure of these 2-carbon entities has so far escaped elucidation.

In spite of the fact that the concentration of acetate or "acetyl" structures present in the body at a given instant is so minute as to render detection very difficult, there is evidence that a large mass of 2-carbon structures is formed in the course of metabolism. Thus isotopic dilution studies in the rat indicate that as much as one per cent of the body weight may exist in this form over a 24-hour period. The potential supply of "acetyl," then, is very large.

Upon the basis of these and other observations it is tempting to employ a tentative working hypothesis to account for some of the disturbances of cholesterol metabolism which are observed clinically. It might be suggested that the balance between the process of synthesis, destruction, absorption, and excretion is only qualitative. Those situations attended by marked increase in the production of certain 2-carbon-fragment ("acetyl") groups in the body might result in a larger mass of substrate becoming available for cholesterol synthesis, and hence hypercholesterolemia as a manifestation. Thus high-fat diets and diabetes mellitus might well be

expected to be accompanied by increases in circulating cholesterol. In those disorders in which oxidative metabolism is increased, the competition for oxidative disposal of "acetyl" depresses cholesterol synthesis with attending hypocholesterolemia, as, for example, in hyperthyroidism. On the other hand, depression of oxidative disposal might conceivably improve the opportunities for employment of "acetyl" in cholesterol synthesis, and thus account for the hypercholesterolemia of myxedema. If the site of synthesis is largely in the liver, the hypocholesterolemia of severe liver insufficiency could be accounted for.

In a number of disorders attended by alterations in cholesterol concentration, it is difficult to indict the synthetic mechanism. Thus the hypercholesterolemia of certain lipoidoses, and that of acute biliary obstruction, have been ascribed to depressed destruction due to unknown causes.

Deposition of cholesterol and cholesterol ester in abnormal quantities in blood vessels, and in the skin, occurs with prolonged hypercholesterolemia. The composition of the lipid so deposited, in the case of atheromas, appears to be secondary to such deposition. In those disorders in which lesions containing cholesterol and cholesterol esters occur with normocholesterolemia, local factors must at the present time be indicted, rather than a fundamental derangement in cholesterol metabolism.

#### AEROBIC OXIDATION

**1. The Krebs Cycle.** The final oxidation of pyruvic acid is accomplished principally by means of the Krebs tricarboxylic acid cycle. Pyruvate or a decarboxylated acetyl or acetate-like derivative ("2-carbon fragment") condenses with oxalacetic acid to form a 6-carbon tricarboxylic acid, cis-aconitic acid, with release of one mole of  $\text{CO}_2$ . By addition of water, isocitric acid is formed which is in equilibrium with citric acid, the latter possibly acting as a governor of the over-all speed of reaction of the Krebs cycle. Isocitric acid is then oxidized to the 5-carbon dicarboxylic acid, alpha-ketoglutaric, with release of a second mole of  $\text{CO}_2$ . Further oxidation results in the formation of the 4-carbon succinic acid and release of the third and final  $\text{CO}_2$  of the original pyruvate. The succinic acid is then reoxidized to oxalacetic, and the cycle is ready to start over again. The reactions producing  $\text{CO}_2$  require di-phosphothiamine as a coenzyme, and the various

oxidations are accomplished by protein dehydrogenases employing phosphopyridine nucleotide or riboflavin nucleotide as coenzymes. The chief features of the tricarboxylic acid cycle are illustrated in figure 37.

It is of particular interest that this cycle, or a portion of it, is probably the final common path for much of protein and fat metabolism; i.e., in the sequence of degradation of protein and fat molecules, substances which are the components of the cycle are formed, and their subsequent fate is identical with that of these same compounds which arise from carbohydrate metabolism (fig. 37). These reactions, for the most part, liberate energy; and it appears that much of this energy may be employed in establishing phosphorylations—e.g., the reconstitution of energy-rich phosphate bonds. Thus this energy is used in part to drive reactions which require an input of energy to proceed.

It now appears that pyruvate, by reactions involving gain or loss of  $\text{CO}_2$  and hydrogen, is in equilibrium with members of the tricarboxylic cycle such as oxalacetate (fig. 37), malate, and perhaps acetate, thus providing a means for formation of this very reactive substance, as well as other means for its disposal by the final common path. It should be pointed out that it is likely that the cycle just described will be considerably modified or extended, as further knowledge is gained in the future. On the other hand, it is unlikely that the principles which it illustrates will need to be revised.

**2. Disposal of Hydrogen Atoms and Electrons.** This process, at the present time, can only be described in principle rather than in precise detail. Most of the oxygen which becomes reduced to water in the body does so by virtue of transfer of electrons to it in the final reaction of metabolism by the respiratory catalyst cytochrome oxidase, which has obtained the electrons from cytochromes A, B, and C. Such "activated" oxygen then combines with the hydrogen ions from which the electrons were taken, to form water. The mechanism is represented schematically in figure 37 (below dotted line). It is noted that the phosphopyridine nucleotides (DPN, TPN) are represented as being reduced by hydrogen (electrons) arising from substrates in the aerobic cycle, and as being reoxidized by a transfer of hydrogen (electrons) to the oxidized form of a riboflavin dinucleotide. The flavinedinucleotide

in its reduced form is capable of being oxidized by, and hence of reducing, the oxidized forms of cytochrome (particularly cytochrome C), the latter being in turn reoxidized by cytochrome oxidase, which is in its turn reoxidized by virtue of transferring electrons to oxygen. The reactions of the cytochrome system are all electron transfers with the corresponding hydrogen atoms, from which the electrons were taken, existing transiently in the internal environment as hydrogen ions. It is likely that in some instances the path of the electrons involves the other cytochromes (A, B) in a manner analogous to a bucket brigade, but it is the oxidase which accomplished the final transfer to oxygen.

Certain flavine nucleotides may themselves reduce molecular oxygen, but in this case the product is hydrogen peroxide, not water. Practically all cells contain one or both of two other ferroheme catalysts, peroxidase and catalase, which prevent accumulation of peroxide by converting it to water and nascent oxygen, or water and molecular oxygen, respectively.

A considerable amount of the energy from degradation of foodstuffs is converted into mechanical energy employed in muscular contraction. The mechanisms of this process are not yet entirely known, but it is clear that hydrolysis of ATP plays a central role, and is the immediate source of energy supporting the process in the muscle fiber, either in terms of causing contraction, or more likely in bringing about "relaxation" following contraction. This requires the continuous reconstitution of ATP by means already mentioned. If these processes fail to keep pace with ATP hydrolysis, the stores of creatine phosphate in the muscle are employed as a substitute, these subsequently being reconstituted by phosphorylation by ATP or other energy-rich phosphate donors, when the demand for ATP or creatine phosphate bond energy in the muscle fiber has declined to normal (i.e., during the "resting" state).

By far the largest fraction of the total energy obtained by degrading glycogen to  $\text{CO}_2$  and water is that released in reactions subsequent to pyruvate formation. Anaerobic energy, when required in large amounts, is obtained at the expense of gross depletion of glycogen stores and lactic acid accumulation—phenomena which ac-

company, for example, sudden violent exercise.

It should be emphasized that this brief description does not portray all of the mechanisms by which  $\text{CO}_2$  and water arise from the degradation of glucose-6-phosphate, but includes only pathways which are probably of quantitative importance, and which indicate the principles involved. The anabolic aspects in terms of resynthesis of glycogen from the various degradation products of glycogen or from other metabolites, including  $\text{CO}_2$ , cannot as yet be clearly outlined, although such resynthesis is known to occur. In this regard the anaerobic glycolytic cycle is known now to be entirely reversible, and may well be the path of resynthesis, once the metabolite concerned has been converted into pyruvic acid or some earlier member of the cycle.

Certain possible points of entry of fat and protein into the final common metabolic path are indicated in figure 37. This serves to demonstrate the ease, as well as the complexity, of the interconversion of the major foodstuffs. It also serves to indicate the variety of consequences of dislocation in the rate, or inhibition, of one or more of the reactions by which  $\text{CO}_2$  is evolved and hydrogen atoms are disposed of. Thus the presence of cyanide, which poisons cytochrome oxidase, instantly reduces respiration and energy production to a minute fraction of its original value, and the metabolism of all foodstuffs is involved. But in addition to this sort of effect, various reactions of synthesis which require energy may be impaired when any dislocation occurs, and the overall result is alteration in physiologic function and morphologic change in the tissue concerned.

#### CERTAIN ASPECTS OF THE ROLE OF THE LIVER IN METABOLISM

It has been pointed out that the recent evidence strongly suggests that practically all of the glucose in the blood during fasting is derived from the breakdown of liver glycogen. In the liver two processes, the formation of glycogen from glucose (glycogenesis) and the breakdown of glycogen into glucose (glycogenolysis), may both take place. The relative velocity of these two processes is the determining factor in the level of fasting blood sugar because it appears that the rates of removal of glucose from the blood, and of its utilization in the periphery, are constant for any given level of blood sugar and insulin action. To understand the levels of blood sugar

encountered in abnormal conditions, and in the interpretation of glucose tolerance curves, clear comprehension of the factors which govern the relative rates of glycogenesis and of glycogenolysis is essential. When the liver is functioning normally, a rise in the blood sugar level causes inhibition of glycogenolysis and stimulation of glycogenesis. A decline in the level of blood sugar has the reverse effect. Similarly, in the peripheral tissues, and more particularly in the muscles, there is an increase both in glycogen formation and in glucose utilization as the result of an elevation of blood sugar.

The effect of insulin is quite similar to the effect of a rise in blood sugar, except that insulin enables phosphorylation to proceed at a given rate at a lower blood sugar level than otherwise. This effect of insulin is brought about by facilitation of the transformation of glucose to glucose-6-phosphate, which is a necessary preliminary step both for glycogenesis and for glycolysis.

The effect of certain hormones from the adrenal cortex and from the anterior pituitary is the reverse of the effects of insulin. The latter hormone inhibits the breakdown of protein and of fat, and favors the utilization of glucose, thereby tending to lower the blood sugar. On the other hand, the hormones from the pituitary and adrenal have the reverse effect, facilitating the gluconeogenesis from protein and fat, and tending to raise the blood sugar. Thus the blood sugar level is the balance of these antagonistic actions. The exact role of the thyroid is still uncertain, but the clinical observation of a tendency toward elevation and depression of blood sugar levels in the respective states of increased and diminished thyroid activity suggests strongly that this gland, like the pituitary and adrenal, affects carbohydrate metabolism. Such effects are probably relative to absorption of glucose, and hepatic glycogenolysis.

Important evidence concerning the relationship between the liver and the blood sugar has been derived by comparing the response of dogs subjected to pancreatectomy with that of such animals subjected to hepatectomy. If a depancreatized dog be given insulin and glucose at a constant rate, in quantities just sufficient to maintain a normal level of the blood sugar, and then is subjected to a glucose tolerance test, thereby receiving additional glucose rapidly by vein, the resulting curve is of the normal rather

than the diabetic type. Such an experiment indicates clearly that the amount of insulin normally present is sufficient to take care of the additional glucose in a normal fashion, and that additional quantities of insulin are not needed. When, on the other hand, a similar procedure is carried out in an animal from which the liver has been removed, the blood sugar curve obtained after the administration of additional glucose is definitely of the diabetic type. This indicates that the low level of the normal curve is dependent on the rapid storage of glucose as liver glycogen, and not on utilization in the peripheral tissues. Although phosphorylation of glucose and, hence,

the presence of insulin, is necessary for utilization or storage of glucose in the muscles, it appears that even a very small amount of insulin—much less than that ordinarily present—is sufficient for this purpose, and that the important defect when insulin is deficient is in the rate at which the liver can manufacture glycogen from the blood sugar. The important factors governing the level of blood sugar are illustrated in figure 38.

The analogy has been drawn by Soskin and Levine between a temperature-thermostat-furnace system and the blood sugar-hormonal balance-liver system. In such a scheme the level of the blood sugar corresponds to the temperature

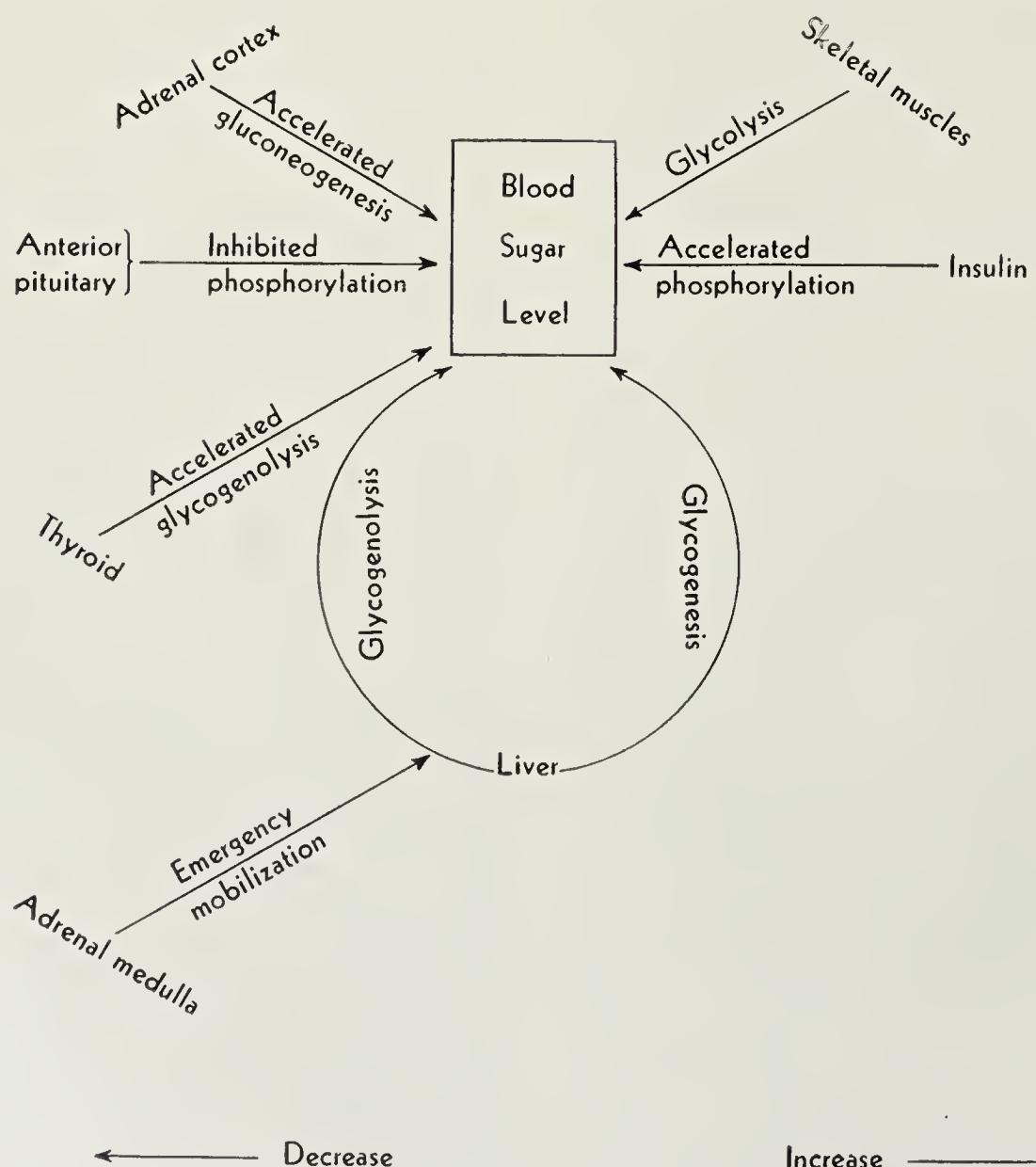


FIG. 38. Factors affecting the level of blood sugar. The factors tending to increase blood sugar—i.e., to push toward the right—are shown at the left. The factors tending to decrease blood sugar—i.e., to push toward the left—are shown at the right. Theoretically, an increase in blood sugar may be brought about either by an increase in the forces on the left, or by a decrease in the forces on the right. Likewise, a decrease in blood sugar might occur as the result of the opposite changes. It is important to note that the liver may act in either direction, depending on the relative rates of formation and breakdown of hepatic glycogen.

of the house. The liver corresponds to the furnace but differs, of course, in that it can store sugar as well as liberate it. The setting of the thermostat is determined by the balance between insulin on the one hand, tending to set the thermostat at a low temperature, and on the other, the adrenal cortical and anterior pituitary hormones, tending to set it at a high level. Such an analogy helps to clarify the concept that the blood sugar, its own level determined by the relative rates of hepatic glycogenesis, glycogenolysis, and peripheral utilization, at the same time tends to regulate the respective rates at which these processes proceed. This concept also clarifies the important regulatory influence of the endocrine glands which determines the sensitivity of the liver (furnace) to the regulating effect of the sugar (temperature).

### MECHANISMS OF CERTAIN DISORDERS OF INTERMEDIARY METABOLISM

#### HYPERGLYCEMIA AND DIABETES

The theoretically possible mechanisms which lead to hyperglycemia, in the light of present knowledge, would seem to be as follows:

**1. Physiologic causes**, including:

- a. the ingestion of large quantities of glucose, and
- b. the rapid mobilization of glucose from the liver as the result of emergency mechanisms acting through the nervous system or the adrenal medulla.

**2. Pathologic causes**, including:

- a. deficiency of insulin, which could result either in diminished phosphorylation of glucose or in accelerated gluconeogenesis, or both;
- b. increased rate of formation of glucose as the result of accelerated gluconeogenesis or glycogenolysis consequent to increased activity of the anterior pituitary, adrenal cortex, or thyroid;
- c. disorders of the liver, acting in such a way as to cause glycogenolysis to proceed more rapidly than glycogen storage or glucose utilization; and
- d. disorders of the central nervous system.

Most of these mechanisms are, in fact, known to occur and are illustrated by various diseases. Thus the rapid rise of blood sugar under conditions of stress, mediated through the effect of the adrenal medulla on the liver, is well known, and it is probable that the hyperglycemia which occurs in certain focal disorders of the nervous system may be brought about by such a mechanism. Many patients manifesting hyperactivity of the anterior pituitary gland, the adrenal cortex, or the thyroid gland are found to have hyperglycemia either in the fasting state or following ingestion of glucose.

Whether insulin deficiency actually leads to diminished utilization of glucose in the peripheral tissues is still a disputed matter, but there is convincing evidence that such a mechanism is not the sole cause of diabetic hyperglycemia. Thus the depancreatized dog has been shown to be able to utilize glucose at a normal rate when the blood sugar is maintained at the excessively high diabetic level, under which condition the rates of phosphorylation presumably approach normal. At a normal level of blood sugar the depancreatized animal is not able to utilize glucose in the periphery at as rapid a rate as the normal animal. Modern investigation seems to have established the validity of the concept that the chief difficulty in the depancreatized animal is the inability to store hepatic glycogen.

The exact etiology and pathogenesis of diabetes mellitus as seen in man still remains a mystery. However, it seems apparent that, regardless of the initiating disturbances, diabetes is due to a disorder of the balance between insulin on the one hand, and the other internal secretions which are antagonistic to insulin on the other hand. Anything which disturbs the balance sufficiently severely may lead to the clinical picture of diabetes, and in all instances the administration of insulin tends to restore the balance, regardless of whether absolute deficiency of insulin or relative deficiency consequent to excessive action of other hormones is the initiating cause.

#### KETOSIS

It has been pointed out already that the production of ketone bodies occurs either entirely, or almost entirely, in the liver, and that the utilization of these substances takes place in the periphery. The rate of formation of ketone bodies appears to be accelerated when glycogenolysis has caused depletion of hepatic glycogen stores. As long as glycogen synthesis and breakdown are proceeding at normal rates in the liver, the products of carbohydrate catabolism take preference in the oxidative enzyme systems, and a brake is maintained on the destruction of fat. Uncon-

trolled fat catabolism appears to occur in the liver when the stores of glycogen are sufficiently diminished. The conditions which may cause ketosis are, therefore, those in which the rate of glycogenolysis is increased, or glycogenesis is decreased, with accompanying absolute or relative lack of hepatic carbohydrate.<sup>4</sup> Such conditions include (1) starvation, either as the result of lack of food intake or excessive vomiting; (2) the excessive ingestion of fat, with corresponding reduction of carbohydrate intake; (3) disorders of liver function, including primary diseases of the liver, and also injury resulting from severe infections or intoxications; and (4) any of the conditions which have been mentioned above as causes of hyperglycemia. It should be pointed out that in all of these conditions, with the exception of diabetes mellitus, the ketosis tends to be remedied readily when adequate amounts of glucose are supplied. However, in the case of diabetes mellitus the administered glucose cannot be readily utilized by the liver for the storage of glycogen and the consequent inhibition of ketone production, unless insulin is supplied also. (At very high levels of blood sugar, glycogenesis may proceed at a normal rate, even in the absence of insulin. The chief effect of the hormone appears to be in enabling phosphorylation reactions to proceed at the relatively low normal glucose level, at a rate which could otherwise be attained only by the mass action effect of excessively high blood sugar levels.)

Theoretically, one might expect that insulin would be useful in all forms of ketosis. However, such is not the case. In the absence of diabetes the amount of insulin already present is sufficient to permit phosphorylation of glucose in the liver. Indeed, the administration of additional insulin is not only useless but may actually be harmful, for the hormone diminishes liver glycogen when it is given to normal animals. On the other hand, in the diabetic individual the supply of glucose is already adequate, and it is the insulin which is needed in order to overcome ketogenesis. Obviously, hypoglycemia may result unless glucose is supplied when, as the result of insulin, the blood sugar begins to decline.

<sup>4</sup> Von Gierke's disease is an exception to this general statement. In this disorder ketone production may become excessive in spite of large stores of glycogen in the liver. Recent evidence indicates that the fundamental difficulty is an enzyme deficiency with absent or diminished capacity to convert glycogen to glucose.

There is a controversy as to whether glucose should be administered in large quantities to all patients in diabetic coma, from the very inception of treatment. Without going into the merits of the opposing arguments, it may be pointed out that all are agreed that once the blood sugar begins to approach the normal level in such a patient, further insulin administration should be accompanied by the administration of glucose. In such a patient with severe diabetes, glucose is needed not only for immediate oxidative purposes, but also to restore the markedly depleted quantities of muscle and liver glycogen, which may amount to several hundred grams.

### HYPOGLYCEMIA

Since the blood sugar is immediately derived from the breakdown of glycogen in the liver, it is evident that any condition which retards glycogenolysis will tend to produce hypoglycemia. The relative rates of glycogenesis and glycogenolysis in the liver are ordinarily controlled by the level of the blood sugar. Following the ingestion of carbohydrate the rise in blood sugar which occurs inhibits the breakdown of liver glycogen, and consequently the blood sugar, following the initial rise, undergoes a decline. Since there is normally a time lag in the response of the liver to the lowered level of the blood sugar, glycogenesis continues to be inhibited and hence the level of glucose in the blood is commonly found to be less two and a half to four hours after the ingestion of carbohydrate than in the fasting state. The degree to which this late postprandial decline in blood sugar occurs varies considerably in different persons, and in a fair percentage of normal people it is sufficient to induce mild symptoms.

The previous diet is also of great importance in determining the level of blood sugar following meals. Individuals who have been in the habit of taking large amounts of carbohydrate appear to have a relatively insensitive mechanism of hepatic glycogen breakdown and a correspondingly accelerated rate of glycogenesis; hence in such persons the degree of decline of blood sugar two to four hours after ingestion of sugar is apt to be marked. On the other hand, either starvation or a diet low in carbohydrate tends to lead to a state in which the blood sugar curve following the ingestion of carbohydrate remains at a relatively high level for a longer time, and the late post-

prandial decline in blood sugar is minimal or absent.

The majority of instances of mild hypoglycemia are, therefore, to be related to the individual's previous dietary habits, and particularly to a high-carbohydrate diet. When, however, there is a disturbance in endocrine balance, hypoglycemia of greater degree may occur. This may be brought about either by an absolute increase in insulin, such as occurs in individuals with tumors of the islet cells, or by a relative increase in insulin in relation to the other hormones which influence carbohydrate metabolism. Thus a deficiency of the thyroid is commonly associated with moderate lowering of the blood sugar, the effect being apparently dependent on diminished rate of glucose absorption and decline in hepatic glycogenolysis. Deficiency of the adrenal cortical hormones appears to decrease the breakdown of protein and to diminish the supply of glucose from this source. Adrenalectomized animals may maintain normal levels of blood sugar and of tissue glycogen so long as they are well fed and not subjected to stresses. However, short periods of fasting tend to result in marked deficiency of tissue glycogen and of blood sugar in such animals. Since, under the same condition, the amount of nitrogen in the urine is likewise diminished, it would appear that the adrenal cortical hormones are necessary in order for the catabolism of tissue protein to proceed normally, and for the glucose formation to occur from this source. Furthermore, there is some evidence that these hormones are concerned in determining the amount of activity of liver arginase, an enzyme involved in the formation of urea from the amino group of amino acids. It may be that they are concerned in the formation of glucose from fat, and that this mechanism likewise is deficient when adrenal cortical hormones are lacking.

Deficiency of the hormones of the anterior pituitary likewise produce hypoglycemia. Ordinarily, the secretion of the anterior pituitary gland inhibits the rate at which the hexokinase enzyme catalyzes the formation of hexosephosphate from glucose, with insulin acting to release this inhibition. In the absence of the anterior pituitary hormone, phosphorylation proceeds too rapidly, and glucose is removed at a rate faster than normal from the blood into the liver and muscles. Hence marked hypoglycemia may occur when the anterior pituitary secretion is deficient,

and it is probable that such a deficiency likewise tends indirectly to produce hypoglycemia through effects on the adrenal and thyroid glands, since the activity of both of these is regulated to some extent by the pituitary hormones.

Aside from the effects of a high-carbohydrate diet in tending to induce secondary hypoglycemia following the postprandial hyperglycemia rise, and in addition to the similar effects of endocrine disturbances, disorders of the liver may lead to marked hypoglycemia. Slight degrees of liver disease may tend to cause hyperglycemia as the result of a stimulating effect on the rate of glycogenolysis and diminution in the rate of and capacity for glycogenesis. With more advanced liver disease the glycogen stores become inadequate to maintain the blood sugar, and hypoglycemia tends to occur in the fasting state which may be converted quickly into hyperglycemia by the administration of glucose. The liver in such an individual is unable to convert the administered glucose to glycogen at the normal rate, and hence hyperglycemia occurs when glucose is given. On the other hand, in the fasting state the liver is unable to keep the blood sugar at the normal level because of the deficiency of glycogen stores. Ordinarily, hypoglycemia of hepatic origin does not occur except in the presence of rather advanced liver disease. The phenomenon is, therefore, likely to be a serious prognostic sign.

The normal levels of tissue glycogen for liver, skeletal muscle, heart, and brain are in the general region of 5, 1, 0.5, and 0.1 per cent, respectively. The small amount of glycogen which is present in the brain seems to be bound in structural compounds, and to be relatively unavailable for oxidative purposes. Such being the case, it is not surprising that the brain is the organ which suffers predominantly when the blood sugar is abnormally low. The chief symptoms of hypoglycemia are weakness, faintness, dizziness, psychic irritability, hunger, sweating, palpitation, tachycardia, alterations in blood pressure, and, in severe cases, unconsciousness followed by convulsions. Most of these manifestations appear to be either the direct result of the diminished amount of glucose available for cerebral oxidation, or the indirect result of stimulation of adrenal medulla with release of epinephrine. The latter mechanism is probably responsible for the pronounced symptoms referable to the cardiovascular system which occur in many patients

subject to attacks of hypoglycemia. Certain recent evidence indicates that, during hypoglycemia, acetylcholine synthesis is increased in nervous tissue, and that the "central" effects of hypoglycemia are due to an excess liberation of acetylcholine.

The symptoms of hypoglycemia and the differentiation of this condition from other states which may simulate it are discussed in more detail in Chapter 7.

### THE FATTY LIVER

In order for chemical transformations to proceed normally in the body, it is of prime importance that the liver function properly. The multiplicity of chemical reactions occurring in this organ is indicated by the fact that from 20 to 40 per cent of the total oxygen consumption of the body takes place there. The healthy liver has a large glycogen store, and conditions which injure the liver, whether they be primarily of bacterial or of chemical origin, tend to reduce hepatic glycogen and to increase the amount of fat and cholesterol ester in the liver. An understanding of the role of the liver in fat metabolism is, therefore, of the utmost importance in the treatment of liver disease.

Liver fat is derived from three sources—the diet, the peripheral fat depots, and synthesis within the liver. Normally, the rate of appearance of fat in the liver is in approximate equilibrium with its rate of removal either by oxidation or transportation for storage in peripheral depots. Several factors are involved in the maintenance of this equilibrium, disturbance of any one of which may result in a piling up of fat in the liver.

This equilibrium is shown graphically in figure 39. Synthesis of fat by the liver is stimulated by cystine and thiamine. Absorption of dietary fat is dependent on the amount in the diet and the functional integrity of the intestinal mucosa and the various lipases, detergents, and vitamins, probably including inositol, in the intestines. The maintenance of normal electrolyte composition of the intestinal mucosa by the adrenal cortical hormones is also essential for normal fat absorption.

Removal of absorbed and synthesized fat is accomplished by transportation to the peripheral depots via the serum in the form of the choline-containing phospholipid, lecithin, cholesterol es-

ters, and fatty acids. This process is largely dependent upon an adequate supply of choline, or methionine from which choline can be derived, the so-called lipotropic substances since they are necessary for the formation of lecithin, the principal serum phospholipid, by the liver.

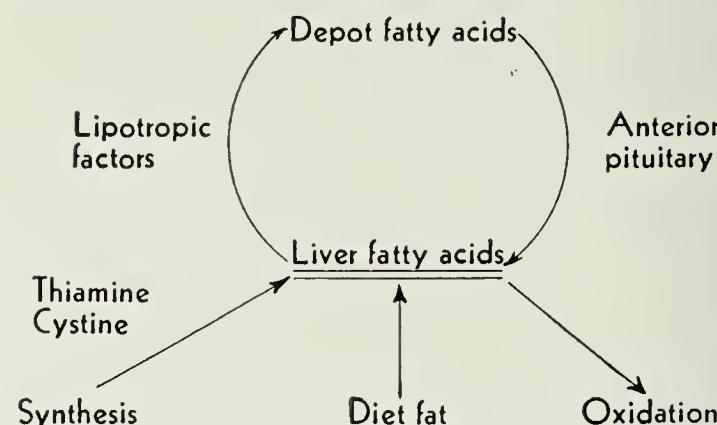


FIG. 39. A graphic representation of some of the chief factors governing fat metabolism.

Fat is returned from the peripheral depots to the liver under the influence of a hormone from the anterior pituitary gland, probably the so-called ketogenic hormone, which in turn is regulated by the energy requirements of the peripheral tissues demanding fat for oxidation.

Thus it is apparent that fatty livers may result from increased synthesis by the stimulation of excessive amounts of cystine or thiamine; by increased absorption from excessive dietary fat; by decreased removal as a result of a deficiency of lipotropic factors, as is seen in the dietary deficiencies associated with alcoholism and pellagra; or by the excessive activity of the anterior pituitary in bringing fat from the depots at a rate faster than it can be oxidized, as occurs in unregulated diabetes or malnutrition, when the tissues are in need of energy.

Throughout the foregoing chapter the importance of enzyme systems and of hormones, which act by affecting such enzyme systems, has been emphasized. It should be pointed out that knowledge in this regard is still quite limited, and that it is highly probable that in the near future important advances in the understanding of the mechanisms of disease, and consequent improvements in therapy, will be achieved by further progress in this direction.

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## Section 5—Electrophysiology

# 31

## Electrical Properties of Tissue. The Electrocardiogram

Hans H. Hecht and Lowell A. Woodbury

The Cell  
Excitation  
Conduction  
Volume Conduction  
Nature of Excitation and Recovery, Illustrated on Cardiac Tissue  
Rhythmic Properties of Tissue: Refractory Period, Re-entry, and Theory of Circus Movement  
Nature and Spread of Cardiac Excitation  
Nature and Spread of Repolarization: Recovery Phase  
Spread of Current Through Body Tissue. Electrocardiographic Leads  
Spread of Current Through Body Electrocardiographic Leads  
Form of Normal Electrocardiogram  
Normal Pattern  
Cardiac Vectors, Area of Electrocardiogram, and Ventricular Gradient  
Further Uses of Ventricular Gradient and of Unipolar Limb Leads: Spatial Position of Heart  
Form of Abnormal Electrocardiogram  
Abnormal P Waves  
Abnormal QRS Group  
Primary T Wave Changes (Abnormal T Waves and Abnormal RST Segments with Displacement of RT Junction)  
Abnormal QT Interval  
Combined Pattern: Myocardial Infarction  
Combined Pattern: Ventricular Enlargement  
Combined Pattern: Electrolyte Disturbances  
Appendix: Electroencephalography

### THE CELL

Living cells convert energy and use it to maintain their economy by dynamic steady states. Complex enzyme systems within the cells transform foodstuffs to other more useful forms. Electrolyte patterns within the cell are maintained in spite of different patterns without by obscure "pump" mechanisms. Asymmetric movement of substances across the cell membrane are largely responsible for differences in electrical charges between the inside of the cell and its surrounding environment. Cell membranes are "polarized" so that the interior of the resting cell is electronegative with respect to the outside of the cell.

Cells store potential energy and may be termed irritable. In some "irritable" cells this potential energy can be converted suddenly to other forms. When this occurs a cell is said to

have been excited. Nerve and muscle are classified as excitable tissues and respond with certain propagated pattern ("excitation") to adequate stimuli. This response is of a complex nature, and consists of both electrical and chemical com-

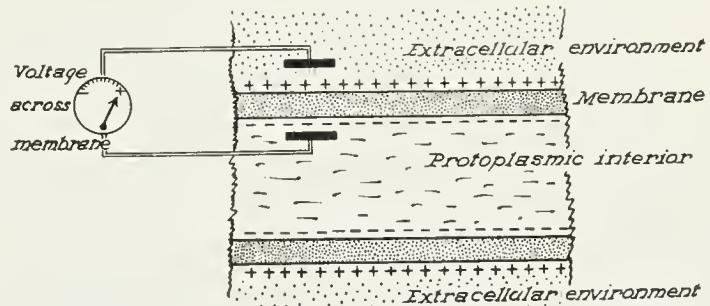


FIG. 40. The cell. The cell consists of an inner core, a membrane, and a pump mechanism or "metabolic battery" which maintains the polarization of the resting membrane with positive electrical charges on the outside and negative charges on the inside of the resting cell.

ponents. The electrical portion is most often studied because of the brief duration of a single response and the greater ease of recording short electrical phenomena.

When only excitation of a tissue is being considered, the basic unit, the cell, may be regarded in a much simpler light than when other actions are studied.

From the standpoint of excitation, the cell consists of an inner electrically conducting core of protoplasm, an outer "polarized" membrane, and a metabolic mechanism or "battery" which maintains the voltage difference between the inside and the outside of the cell (fig. 40). The cell is immersed in the extracellular fluid of the body. This may be considered a weak solution of electrolytes, which acts as a poor conductor of electricity. Such solutions are known as "volume conductors." The membrane of the excitable cell is a highly important structure. It is very thin; estimates of its thickness range from 0.0027 to 0.01 micron. It is polarized with

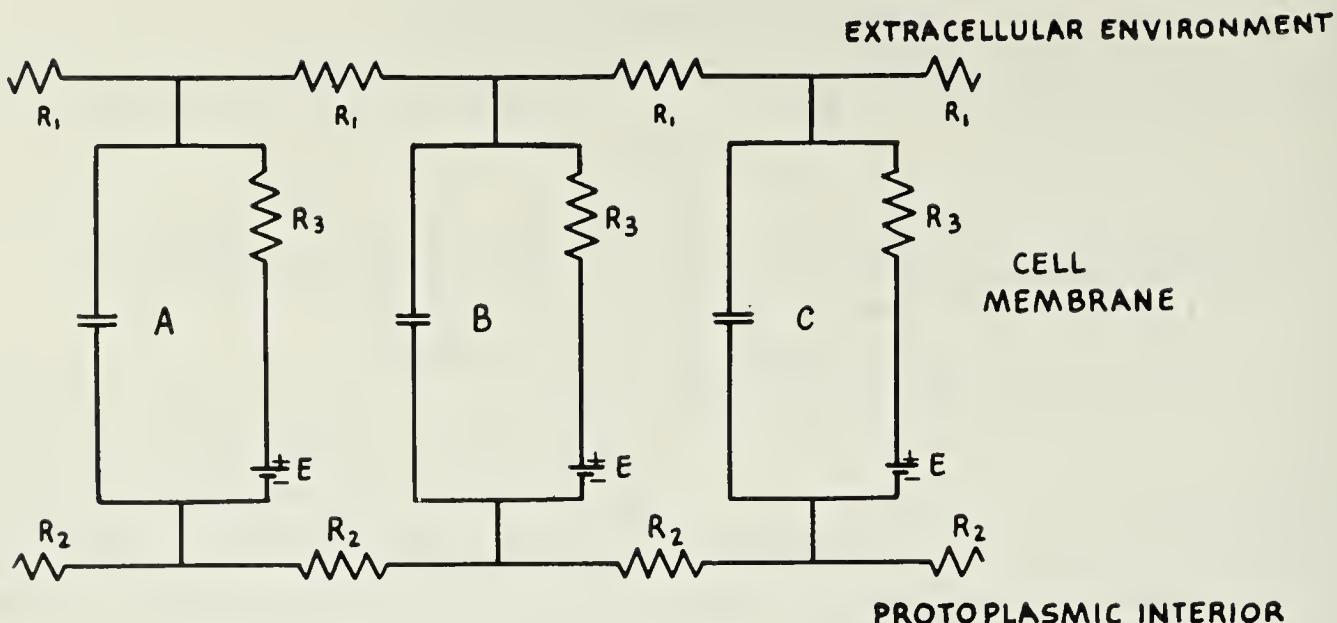


FIG. 41. Circuit diagram of the cell, the membrane, and its extracellular environment. At rest, all condensers (illustrated by parallel lines on the left side of A, B, and C) are charged and no current will flow because all elements (A, B, and C) are at the same potential. If the membrane resistance ( $R_3$ ) of element A is reduced in magnitude, its condenser will discharge. When this occurs, the condenser of element B will discharge through the external and internal resistances ( $R_1$ ,  $R_2$ ) and a current will flow. When the second condenser has discharged by a critical amount, resistance of element B decreases, the condenser of element C discharges, and a current flows from C to B and so forth over an infinite number of elements. (After K. Cole.)

the outside of the cell about 50 to 100 millivolts more positive than the inside. The structure of this membrane is unknown. It is even uncertain that the membrane to which we are referring has any connection with the microscopically visible boundary membrane of the cell.

The cell with its external fluid environment, its polarized membrane, and its internal protoplasmic conductor can be represented in analogy by a combination of electrical resistances, condensers, and batteries as shown in figure 41. Such an analog has a use and serves to explain some of the observed static and dynamic properties of the excitable cell. Another useful though oversimplified analogy, and one perhaps having some resemblance to reality, is illustrated in figure 42. Here, the polarized membrane is considered to consist of polarized lipoid molecules, oriented by the polarizing voltage between the inside and the outside of the cell and thus forming a partial insulator. If for any reason, physical, electrical, or chemical, the voltage across the membrane drops below a certain critical amount, the repulsion of the like charges on the lipoid molecules plus random thermal motion results in a disorientation of the molecular arrangement. With the molecules disorganized, the insulating character of the membrane disappears and a flow of current from adjacent

regions takes place through the "depolarized" region. These adjacent regions then in turn become depolarized and the process continues until the whole tissue has become involved. Upon recovery the metabolic "battery" restores the

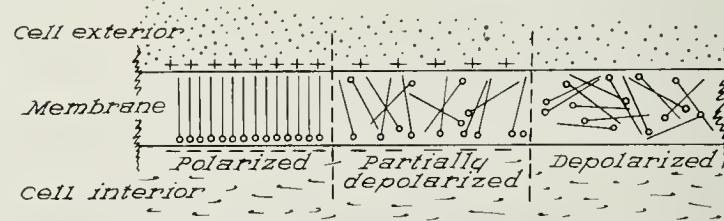


FIG. 42. A molecular concept of depolarization of cells. At rest, the polarizing voltage between cell exterior and interior "orients" (polarizes) the molecular structure of the membrane. Molecular disorganization occurs if the polarizing voltage decreases by a critical amount (see text).

polarizing charges and the molecules reorient under the influence of the polarizing field.

By the use of microelectrodes (0.5 to 1 micron in diameter at the tip) the voltage existing across the cell membrane between the inside and outside of the cell can be measured *in situ*. When the electrodes are connected to a suitable recording system, the variations of the membrane potential can be recorded during the cycle of excitation. The membrane potentials for frog ventricular fibers average about 60 to 70 mv. when measured

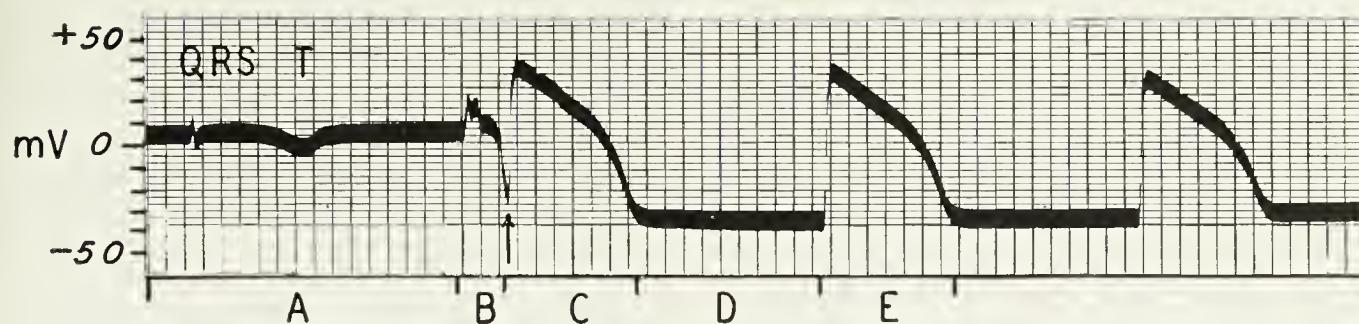


FIG. 43. Membrane resting and action potentials from a single frog ventricular fiber. (A) Base line and surface electroventriculogram; (B) penetration of cell membrane by microelectrode; (C) rapid depolarization of cell showing reversal of membrane polarity at arrow; and slower recovery of polarization, the whole constituting an action potential; (D) membrane resting potential; (E) action potential. Time lines: 0.1 sec. Vertical scale at left: millivolts.

in this fashion. In figure 43 is shown a typical recording of the membrane resting and action potentials. During section A the microelectrode was on the outside of but near to the heart, and a surface electroventriculogram is recorded. This section is the base line. At B the electrode passed through the cell wall just prior to electrical systole of the heart. There is some artifact as the membrane is pierced, followed by a negative deflection. At the arrow the membrane depolarized and the voltage across it fell to zero and then reversed, indicating that the interior of the cell became positive with respect to the outside. The process of recovery then ensued; the reversed membrane voltage returned to zero and built up in the normal direction with the inside of the cell negative to the outside. At the end of C the recovery process was complete. The steady section of the line at D represents the membrane resting potential, and the sections C and E and similar ones represent the membrane action potential. The part of the action potential in which the membrane voltage is reversed may be termed the *overshoot*. When a surface electrocardiogram is taken simultaneously with the membrane potential, it may be seen that QRS corresponds to the period of rapid depolarization and that the end of T is coincident with the end of the recovery phase.

**Excitation.** When an adequate stimulus is applied to a nerve or muscle, the cell "fires" or becomes excited, and a wave of excitation passes along the surface of the cell. The stimulus lowers the voltage over some part of the membrane by a critical amount and this region then depolarizes. This depolarized region acts as a "sink" and a current from surrounding, as yet polarized, areas flows into that region. These adjacent areas constitute a "source." Current from source

areas soon lowers their voltage to the critical point and they in turn depolarize and become "sinks" to other areas. The process continues until the whole excitable cell has been depolarized. This combination of source and sink constitutes an electrical doublet or *dipole*.

A recovery process in which the cell is repolarized takes place thereafter. This may occur almost instantly (within milliseconds) in nerve cells, or not for some time (0.2 to 0.4 second) in heart muscle. When the cell has recovered, it is ready to fire again.

The cell during and after firing goes through a series of changes which are named in terms of excitability. They are: (1) an absolute refractory period, during which the cell cannot be stimulated to fire again; (2) a relative refractory period in which the cell can be fired only by a greater than normal stimulus; (3) a brief supernormal period in which the cell is more excitable than normal; (4) a subnormal period in which the cell is less excitable than normal; and (5) complete recovery. These changes naturally bear some relationship to the degree of repolarization of the cell membrane. Not all of the above-listed stages occur in all types of cells. Supernormality is absent in certain types of nerve fibers, for example, and may be demonstrated for heart muscle only under certain conditions.

**Conduction.** The velocity of the conduction of an impulse along a nerve or muscle depends upon a number of factors such as the diameter of the fiber, the resistance of the surrounding medium, the direction of spread, and the type of tissue. In a nerve or muscle, *in situ* conduction normally occurs in one direction—the so-called dromal conduction. This unidirectional conduction is only an accident of placement, and

conduction can occur readily in the reverse antidromal direction.

Under certain conditions, conduction may be impaired or completely blocked in one direction but not in the reverse (monodromal conduction). In heart muscle an impulse is normally conducted from the region of the sinoatrial node over the atria through the atrioventricular node, down the bundle of His and its branches, and out over the ventricles. However, abnormal impulse may arise from a focus anywhere along this route (nomotopic) or from elsewhere (heterotopic). It can stimulate and send out waves of excitation both dromically and antidromically. Conduction can be blocked by a number of mechanisms such as mechanical pressure, lack of oxygen, inflammatory changes, general and local anesthetics, edema with ion excesses or deficits, metabolic changes in the cell, and other traumatizing influences.

**Volume Conduction.** The conduction of an impulse along a fiber is always accompanied by a flow of current from a source in the polarized region to a sink in the depolarized region. Since the fiber is immersed in the electrolytic volume conductor of the body fluids, the current traverses this comparatively poor "volume conductor." When a current flows through a wire, its route of flow is rigidly channeled by the wire boundaries. In a volume conductor, current flow takes place through the entire volume of the conductor in such a fashion that the resistance from source to sink is at a minimum or, alternatively, so that the current flow is at a maximum. There will therefore be a flow of current throughout the volume of the body which will vary in intensity from region to region in accordance with laws that govern the flow of currents in volume conductors. The current flow may be thought of in terms of lines of current flow originating at the source and ending at the sink. When current flows in a volume conductor under the influence of a voltage, the lines of current flow will be at right angles to the voltage lines. In other words, the existing potential causes the current to flow in the direction of the potential. Imaginary lines can be drawn which will give the position of equal voltage points. These lines are known as *isopotential lines* (fig. 44).

From theoretic considerations involving the flow of current through a volume conductor,

these isopotential lines can be mapped for certain conditions. In figure 44 is shown the distribution of these lines about two small cylinders (the "source" and the "sink") in an infinite volume conductor. The figure represents only the voltage lines. The current lines will be from one cylinder to another and at right angles to the voltage lines.

The source and the sink on a conducting fiber can be regarded as consisting of a band of dipoles analogous to the situation illustrated in figure 54. The current will flow from the positive edge of the dipole band or the source to the negative edge or sink, and the voltage lines will be distributed as indicated in figure 44.

One further point is necessary. In figure 44 it will be noticed that all lines form circles, with the exception of the one marked I, and this may be considered to form a circle at infinity. If a point be chosen at random, so long as it is an appreciable distance from the source and sink, it will be found to be either on or close to the I line. A recording electrode placed on this line will not be influenced by the flow of current if source and sink remain stationary (neutral electrode).

These fundamental properties of the cell submerged in an electrolyte medium form the basis for the interpretation of many of the recorded electrical events of living tissue. Of these, the response of heart muscle and the understanding of the nature and spread of cardiac action current has become of particular concern in clinical medicine (*electrocardiography*). This section will deal primarily with the nature and spread of cardiac action current in normal and abnormal hearts as an example of electrical properties of tissues. The discussion on fundamental properties of cardiac muscle may in many respects be applied directly to the interpretation of the electrical phenomena of other tissues as well. The electrical activity of brain cells has been recorded for many years, and tracings obtained from the skull have been employed extensively in practical neurology, although many details concerning the nature of such records are poorly understood. *Electroencephalography*, however, has its definite place in medicine, and an introduction to its clinical application based on the concepts presented here will be given in an Appendix (p. 392). Action currents of striated

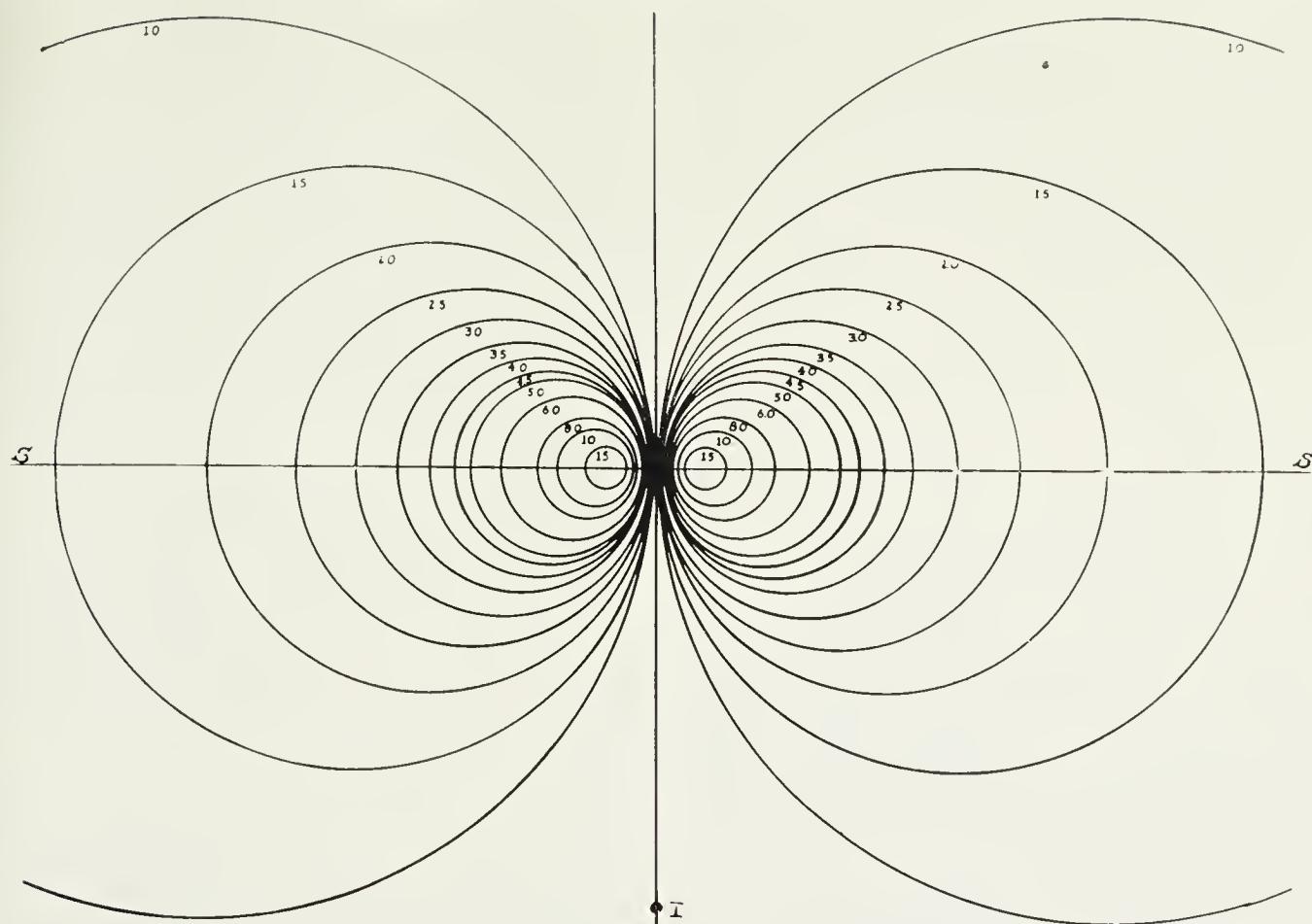


FIG. 44. Concept of dipolar excitation. End-on view of isopotential lines about two small cylinders with a voltage difference between them and submerged in an infinite volume of conducting medium.  $S-S$  represents extension of a line connecting the center of the two cylinders;  $I$  represents the voltage line halfway between the sink and the source which is used as a reference. If the diagram is considered to represent the voltage field about the sink and the source on an excitable cell,  $S-S$  would represent the cell surface, and  $I$  the effective position of a distant ("indifferent") electrode. The figure is plotted from laws governing the flow of current in volume conductors. (Courtesy, Hecht and Woodbury: *Am. Heart J.*, 1950.)

muscle (*electromyography*) have recently become of interest in the evaluation of diseases of muscle, neuromuscular junction, muscular atrophy, and peripheral nerve lesions. A discussion of normal and abnormal muscular reactions, however, exceeds the scope of the presentation at this time.

#### NATURE OF EXCITATION AND RECOVERY, ILLUSTRATED ON CARDIAC TISSUE

**Rhythmic Properties of Tissue: Refractory Period, Re-entry, and Theory of Circus Movement.** A fundamental property of many organs, and particularly of cardiac muscle, is that of rhythmic repetitive impulse formation, discharge, and mechanical contraction. As an example, in cardiac tissue a rhythmic discharge from the sinoatrial node activates the rest of the heart. The property of repetitive impulse formation is not confined to this region, however, and

other sections may initiate such impulses. A hierarchy of rhythmicity exists in cardiac tissue by virtue of the natural rate of impulse formation. The higher regions such as the sinoatrial node fire more rapidly than lower regions, so that under normal conditions the center of highest inherent rhythmicity controls the basic cardiac rate.

Little is known about the mechanism underlying rhythmicity. Various physical models have been evolved to explain, by analogy, such action. The commonest example is that of a *relaxation-oscillator* such as is used in simple electrical nerve and muscle stimulators and in the sweep circuit of oscilloscopes. Figure 45 illustrates such a circuit. It is thought that in any center of impulse formation the cell membranes are unstable and break down periodically, giving rise to an impulse. The recovery process follows, gradually repolarizing the membrane. At the

time of complete recovery the membrane again breaks down and the cycle is repeated. It can be seen that such a process is analogous to a relaxation-oscillator. The reason for the instability of the membrane is unknown, and little

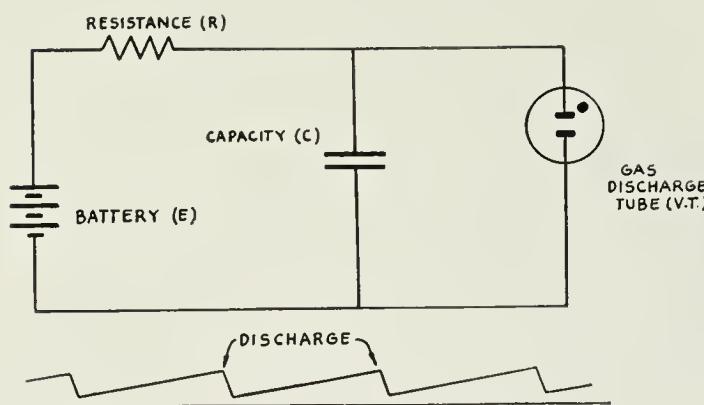


FIG. 45. Rhythmic discharges of an impulse as demonstrated by a relaxation-oscillator circuit. The condenser (C) is charged slowly by the battery (E) through resistance (R) until a critical voltage across the gas tube (V.T.) is reached, at which time the tube suddenly becomes a conductor and discharges the condenser. The cycle is then repeated, giving the wave form illustrated.

factual information can be found. The fact that rhythmic activity is present in such widely varying tissues as smooth muscle, nerve tissue, and cardiac muscle would imply that it was not a peculiarity of the tissue involved.

Two properties appear necessary for rhythmic repetitive impulses: the existence of a steady state or continually active polarized region, with periodically depolarizing membranes and a boundary or threshold between it and the area to be activated. Clinical observation likewise leads to the assumption that an area serving as pacemaker and discharging repetitive stimuli is surrounded by an obstacle, a boundary that is

to be penetrated before propagation of impulses can occur. However, an impulse must be conducted from the pacemaker region into the tissue to be excited. It may fail to do so even while the surrounding tissue remains receptive and while the pacemaker area continues to be active. A block surrounding the area of impulse formation exists which prevents repetitive discharges from reaching the organ. In the heart, the existence of such a *perifocal exit block* is best illustrated in the not uncommon example of *sinoauricular block* (fig. 46) where impulses fail to pass from a presumably active sinus region into the bulk of atrial muscle.

The discussion leads to the problem of *impulse conduction*, a proper understanding of which is a prerequisite to the interpretation of cardiac irregularities (Chapter 235). It will here be considered only in so far as it concerns the nature of certain abnormal cardiac rhythms.

Conduction in the heart both over the cardiac muscle and over the special conducting system occurs by the mechanism described on pages 352-358. It depends on several factors: (1) on the anatomic nature and the glycogen content of tissues to be traversed (high conduction rates in Purkinje network and atrial muscle, moderate in ventricular muscle, slow in nodal structures); (2) on the direction of transmission with respect to muscular structure, conduction being more rapid along than across the muscle units; and (3) on the phase of the refractory period. The first two factors remain relatively uniform over long periods; the last, as stated above, varies constantly during the phases of the cardiac cycle. A correlation between recorded mechanical and electrical events and the phases of responsiveness

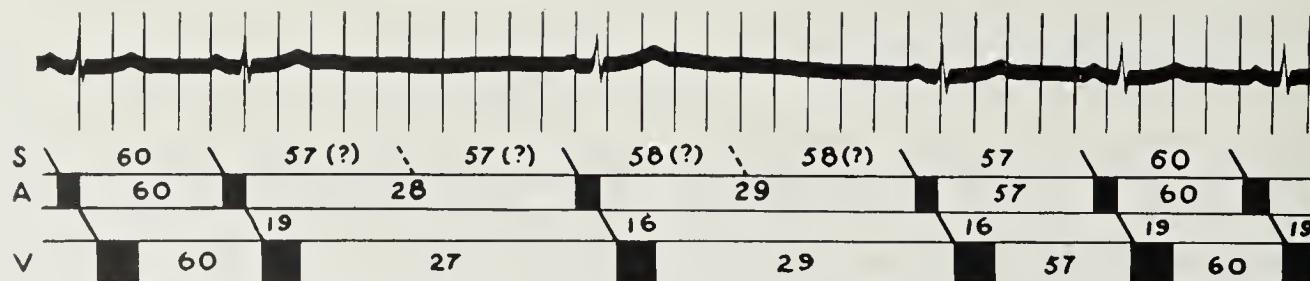


FIG. 46. Perifocal exit block in an example of sinoauricular block. The activity of the sinus node (S) swings around 60 beats per minute. Following the second impulse, the activity of both atria (A) and ventricles (V) suddenly drops to one-half the normal rate for a period corresponding to three sinus impulses, the first and third of which (impulse no. 3 and 5) apparently do not pass the area surrounding the impulse center. The sudden bradycardia results in prolonged rest and improves conduction through the atrioventricular junctional tissue. The PR interval is therefore shortened during the period of block from a previous value of 0.19 second to 0.16 second. (S) Sinus node (impulse center); (A) atria; (V) ventricles. Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

Table 33

## ROLE OF THE REFRACTORY PERIOD OF CARDIAC MUSCLE IN CAUSATION AND MAINTENANCE OF CARDIAC IRREGULARITIES

Site of Action	Refractory Period		Supernormal Period
	Complete	Partial	
Sinus node . . . . .	Auricular standstill	Sinoauricular block	
Atrial muscle . . . . .	Postectopic pause	Linked auricular extrasystoles ("fixed coupling"), paroxysmal tachycardia, fibrillation and flutter	
A.V. node and common branch of bundle of His	A.V. block (complete A.V. dissociation)	Partial A.V. block (P-R prolongation, dropped beats, Wenckebach's periods)	A.V. dissociation with ventricular capture (interference dissociation)
Main branches of conduction system	Bundle branch block	"Incomplete" and "transient" bundle branch block, aberrant responses	
Ventricular muscle . . . . .	Postectopic pause	Linked extrasystoles ("fixed coupling"), paroxysmal tachycardia, aberrant ventricular responses, electrical alternans, fibrillation and flutter	

of cardiac tissue is illustrated in figure 47. For the interpretation of cardiac irregularities, partial refractoriness and/or monodromal conduction is of particular interest (table 33).

Reduced responsiveness during the partial refractory period may manifest itself in various forms. A structure to be traversed by the action current may, as a whole, recover slowly or never completely (*relative refractory period*). Certain simple forms of prolongation of A.V. conduction with a prolonged PR interval (fig. 199), and certainly prolongation of A.V. conduction or complete temporary blockage of conduction following a premature (extrasystolic) stimulus, belong to this group (fig. 48). A structural unit may not respond completely because some of its regions or groups of muscle fibers fail to respond at all while the remainder respond unimpaired (*partial refractory period*). This accounts for the phenomenon of *aberrant response* of ventricular muscle where abnormal beats are recorded only if the preceding diastolic phase was unusually short. The order of excitation is altered because some sections of cardiac muscle in the path of the advancing action current fail to respond, while others do respond. Aberrant responses are frequent in instances of auricular fibrillation with rapid ventricular rates; they contribute to

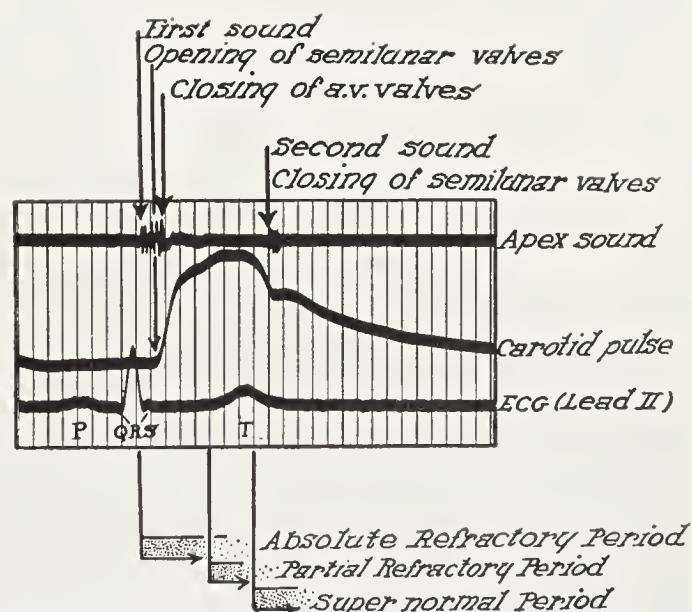


FIG. 47. The mechanical and electrical events of the cardiac cycle.

The first and second heart sounds (upper tracing) define mechanical systole; the carotid pulse wave (middle tracing) reflects pressure changes in the aorta. A simultaneously recorded electrocardiogram (lower tracing) reveals that the onset of electrical excitation of ventricular muscle (QRS) slightly precedes the mechanical events and that the end of T (representing complete repolarization) occurs at the beginning of the second sound and at the incisure of the carotid pulse.

The phases of refractoriness of ventricular muscle are indicated at the bottom. Junctional tissue and the Purkinje system begin to recover during the rising limbs of T; ventricular musculature slightly later.

Time lines: 0.2 second, 10 mm. = 1 mv. Film speed: 25 mm./sec.

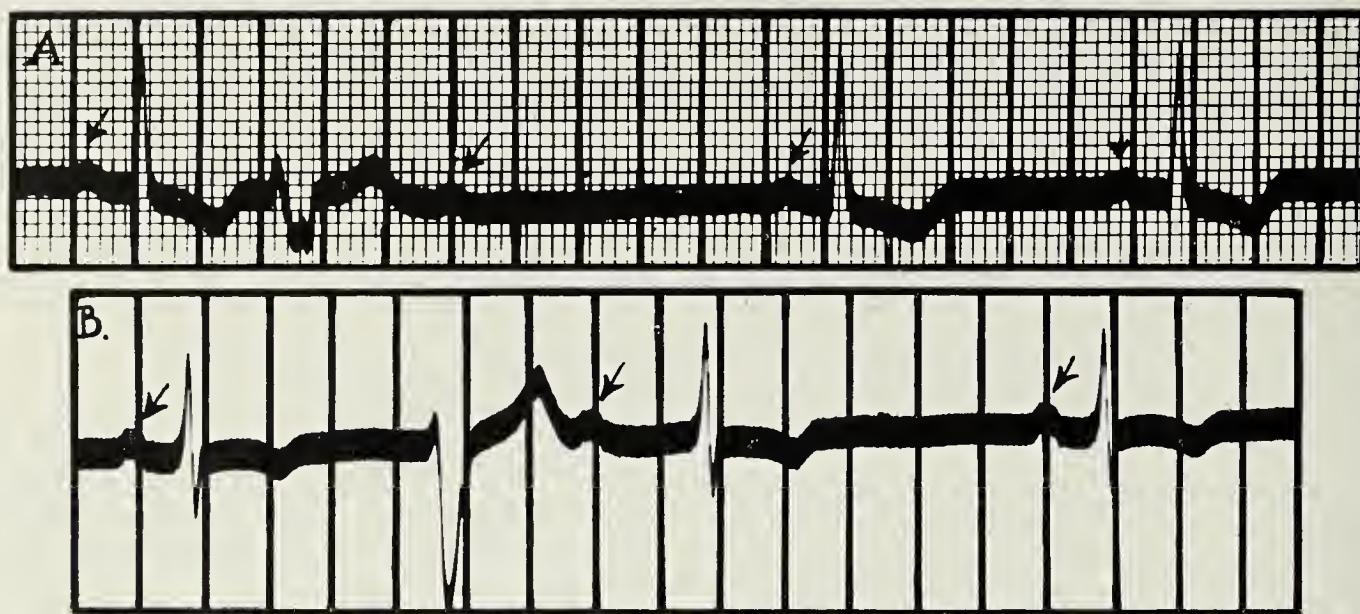


FIG. 48. The refractory period of cardiac tissue.

(A) An early ventricular extrasystole (second beat) causes a state of refractoriness in ventricular muscle or in the A.V. node so that the next normal sinus impulse fails to elicit a ventricular response to a normally spaced P wave.

(B) Conduction through the A.V. node has not completely recovered following the ectopic beat, and a delay in A.V. conduction with a prolonged PR interval results in the first postextrasystolic beat.

Partial or complete A.V. block following an extrasystole with postextrasystolic P waves occurring after the end of the extrasystolic T wave are not normally seen. These records may therefore be considered as examples of minor disturbances in A.V. conduction.

Note "abnormal" shape of the extrasystolic T wave (secondary T wave changes, p. 369).

Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

the abnormal shape of premature beats whether they are on an extrasystolic basis or not; they explain "electrical alternans" and the existence of a "critical heart rate" in certain instances of bundle branch block.

A record displays *electrical alternans* when the form of the ventricular complexes alternates in the face of a regular basic rhythm. Records of this kind are not necessarily associated with mechanical alterations (*pulsus alternans*, Chapter 235). Both, however, are the result of similar basic changes in responsiveness and have, therefore, the same clinical significance. An example of alternans is illustrated in figure 49. Intraventricular conduction defects occurring only above certain critical heart rates (*unstable bundle branch block*—Vesell) are occasionally seen, and unquestionably are the result of slow recovery of conduction in specialized tissue.

Reduced responsiveness or unidirectional block furnishes a clue to the nature of certain extrasystolic disorders and of auricular and ventricular fibrillation or flutter. These explanations are based on the phenomenon of re-entry. Its nature

is diagrammatically illustrated in figure 50, where islets of tissue may not respond to the advancing action current but undergo activation belatedly when the wave of depolarization reaches these islets by a detour. Having now passed through those previously refractory sections of muscle, the original impulse may break

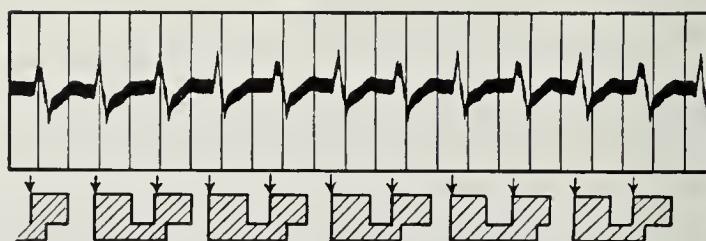


FIG. 49. Electrical alternans. An electrocardiogram (chest lead V<sub>2</sub>) obtained from a 54-year-old patient with hypertensive heart disease and congestive failure. Although a rapid, regular rhythm is present, a definite alternation in the shape of QRS and T waves is seen. The arrows indicate the arrival of impulses at ventricular musculature. The refractory period of various sections of ventricular muscle differs. Certain areas will not have recovered fully and are not, or are only incompletely, responsive to the next following impulse. An aberrant ventricular response will occur. The diagrams indicate the duration of the refractory period. It is evident that the entire ventricular musculature responds only every other beat beginning with the second complex illustrated.

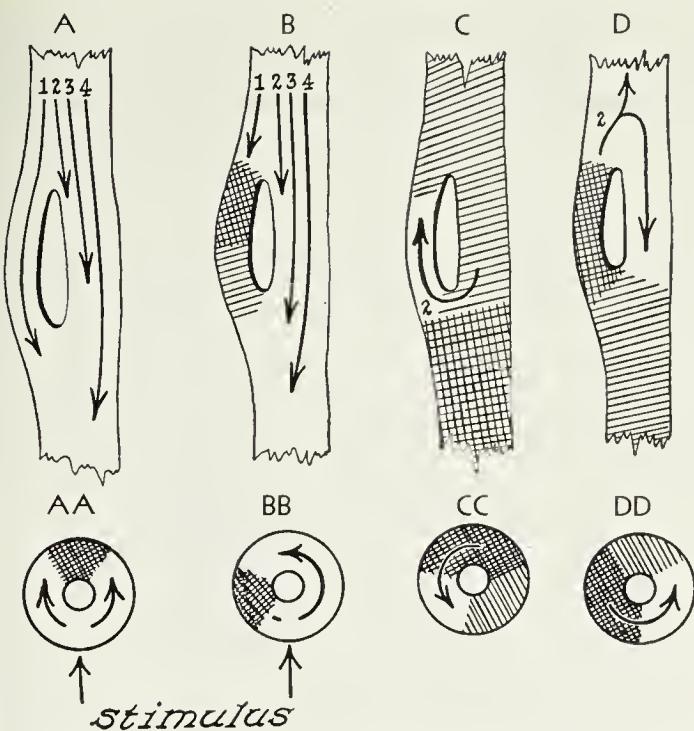


FIG. 50. The genesis of re-entry, circus movement, and extrasystolic disorders with fixed coupling.

Synctytial muscle is illustrated with a small area of impaired responsiveness on the left. Normally (A) activation proceeds smoothly over any of the chosen pathways (1 to 4). If the impulse arrives at a time the local area is still refractory, pathway 1 will be blocked, at least in the above downward direction (B). The original impulse may be able to excite the region somewhat later and from a different direction (2 in C) as the remainder of muscle now enters the absolute refractory period (C). Shortly thereafter, the impulse may break through (D) and re-excite normal muscle that has again completely recovered while the locally depressed region remains refractory. If the latter has not completely recovered at the time the next impulse arrives, continued fixed coupling may occur. If the normal impulse arrives from above at a time when the normal muscle is still completely or partially refractory from the re-entrant beat CC, a continuous "circus" movement may result which is capable of spreading over the entire heart muscle.

The small circles below illustrate the same phenomenon as seen in circular strips of contractile tissue when stimulated at one end. If the stimulus finds its progress barred in one direction it will propagate itself along one limb only (BB). As it proceeds around the circle it may find the originally refractory region responsive (CC), and as a gap of responsive tissue will always precede the wave of excitation, the latter will repeat the circuit indefinitely. All diagrams are based on experimental observations. They were the basis for Lewis' theory of circus movement in auricular and ventricular fibrillation and flutter.

Shaded areas indicate refractory (crosshatched) and partially refractory (hatched) muscle sections.

through into normal tissue and restimulate the heart.

One may postulate that *extrasystolic impulses* (ectopic beats) are of two kinds: (1) They occur if an active region somewhere outside the regular impulse centers discharges impulses irregularly (*common extrasystoles*) or according to an in-

herent regular rhythm that may be faster (*paroxysmal tachycardia*) or slower (*parasystole*) than the primary sinus rate. (2) The regular impulse is slowed in certain regions and re-enters responsive muscle after the absolute refractory period has passed (true re-entry) (fig. 50). This explanation appears applicable for extrasystoles that show a more or less constant time interval to the preceding normal beat ("fixed coupling" and bigeminal and trigeminal rhythms), and has been used to explain the nature of paroxysmal tachycardia.

Incomplete recovery with re-excitation of cardiac muscle has also been assumed as the basis of *auricular and ventricular fibrillation and flutter*. Again the presence of islets of unresponsive or irreciprocally conducting tissue is said to facilitate re-entry, and an impulse, once set up, will continue to circulate through sections of cardiac tissue (fig. 50). This theory of "circus movement" need not, however, be the cause of these irregularities, but it appears likely that partial refractoriness of cardiac tissue with or without re-entry is a prerequisite of such states. There is no doubt that an intimate relationship exists between auricular fibrillation, auricular flutter, paroxysmal tachycardia with and without A.V. block, and simple extrasystoles (see Chapter 235, figure 205). It is still unsettled whether the existence of a relatively large circus excitation underlies these irregularities (Lewis, Wilson) or whether repetitive volleys arising from simple or multiple foci may account for it (Rothberger, Scherf, Prinzmetal). Unusual clinical examples demonstrating the role of reduced responsiveness for the onset of auricular and ventricular fibrillation are illustrated in figures 51 and 52.

The return to full recovery in both nerve and muscle may, under certain conditions, be preceded by a short *phase of supernormal conduction* (fig. 47). It is always present when, in premature auricular beats, A.V. conduction is shorter during the earlier than during the later phase of diastole, and it may explain the not uncommon instances of partial A.V. heart block where only an occasional auricular beat is conducted into the ventricles (*A.V. dissociation with interference*, dissociation with ventricular capture). In such instances the temporary restoration of conduction is usually confined to a period



FIG. 51. The partial refractory period and initiation of auricular fibrillation.

The first and the third sinus impulses are followed by auricular extrasystoles. The first premature systole (arrow) is blocked; the second (arrow) finds both auricular and ventricular musculature partially refractory so that ventricular muscle shows an aberrant response and the auricles begin to fibrillate (re-entrant phenomenon due to partial responsiveness). Following what appears as two ventricular extrasystoles, auricular fibrillation promptly ceases. It may be argued that retrograde conduction from ventricles to auricles occurred which further impaired auricular recovery following the second auricular extrasystole because no episode of fibrillation was noted when the auricular extrasystole was blocked and prevented from passing into ventricular muscle, and auricular fibrillation clearly started after the ventricular response to the second extrasystole. Retrograde conduction following the two ventricular extrasystoles reached an already partially refractory auricular muscle and resulted in a state of absolute refractoriness which terminated the circus movement.

The first ectopic auricular beat followed the normal impulse at 0.30 second, the second extrasystole at 0.32 second. The first was prevented from reaching ventricular muscle because the latter was still absolutely refractory; the second was conducted, but found the conductive system and ventricular muscle only partially responsive: PR of normal beats 0.12 second, of the extrasystolic beat 0.19 second, the relative PR prolongation being followed by a typical aberrant ventricular response. The refractory period of ventricular muscle in this case must therefore lie at approximately 0.31 second.

The figure shows lead V<sub>1</sub> of a 59-year-old male suffering from arteriosclerotic heart disease. Many similar episodes were noted in this patient, most of them initiated by extrasystoles. Time lines: 0.2 second, 10 mm. = 1 mv. Film speed: 25 mm./sec.

in the cardiac cycle that closely corresponds to the period of supernormal conduction as determined by experimental means. Ventriculo-auricular conduction with retrograde P waves following a QRS complex in the face of complete auriculoventricular block has also been explained on this basis.

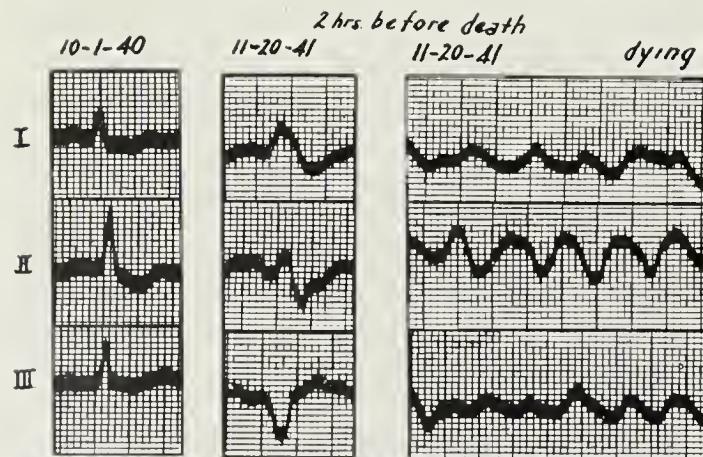


FIG. 52. The partial refractory period and initiation of ventricular fibrillation.

In this patient, a 65-year-old male with arteriosclerotic heart disease, the ventricular complexes widened shortly before death from a previous QRS of 0.09 second to 0.24 second, indicating profound depression of cardiac conductivity. Two hours later terminal ventricular fibrillation was recorded (right-hand curves). It may be assumed that ventricular fibrillation supervened when a regular impulse found the major part of ventricular musculature still partially refractory from the preceding normal beat.

Leads I, II, and III are shown from above downward. Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

**Nature and Spread of Cardiac Excitation.** For the purpose of this discussion the human heart may be divided into two segments: a sheetlike atrial component and a thicker ventricular section. Because of its relative simplicity, depolarization of *atrial tissue* is first considered.

When an electrode attached to one end of a recording galvanometer is placed in contact with atrial tissue while the other is far removed from it, a record is obtained during the depolarization process that is identical to similarly recorded action potentials of isolated nerve and muscle (fig. 53). It consists of a simple biphasic plus-minus potential which at first gradually, then more steeply, rises toward a maximum positive peak. Following this, the curve rapidly reverts to a maximum negative peak, after which it returns gradually to the base line. This response is uniform for all atrial tissue and may be obtained from the human heart *in situ*. If the process of activation may be considered in terms of a current flow from a source to a sink (dipole) with positive charges immediately followed by negative charges, these records permit a simple explanation. As the band of dipoles advances toward the region upon which the electrode has been placed, it becomes more and more positive with respect to distant areas. Maximum positivity is recorded when the "source" has actually reached the region subjacent to the electrode. As it passes over this area a reversal

occurs and a maximum negativity is obtained as the "sink" passes the electrode. In an oversimplified form, the process is diagrammatically illustrated in figure 54.

By assuming that the dipole concept conveniently symbolizes the theory of activation

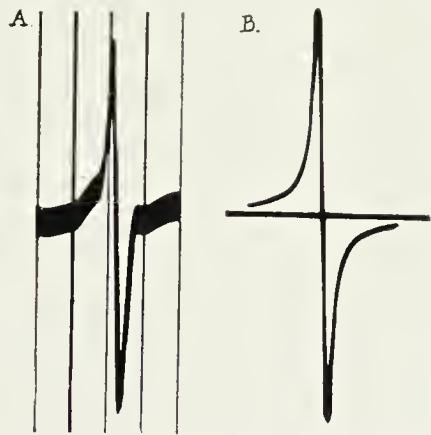


FIG. 53. Action potential of cardiac muscle.

(A) A record obtained by cardiac catheterization from a 58-year-old subject. The recording electrode was in contact with the endocardial surface of the right atrium.

(B) An artificial action potential calculated by placing an electrode in I of figure 44 and moving the other electrode along the line S-S from the extreme right of figure 44 to the extreme left.

The similarities between A and B are inescapable and suggest that the nature of cardiac excitation may be expressed as a series of dipoles moving through a volume conductor (see figure 54). (Courtesy, Hecht and Woodbury: *Am. Heart J.*, 1950.)

of heart muscle *in situ*, the principles of the membrane theory may be carried directly into the field of clinical electrocardiography. The theory is strengthened by the relative ease by which some of the calculated curves and those obtained by experimental means may be duplicated in man. It is opposed to a widespread concept which considers an electrocardiogram as a summation of two somewhat asynchronous "monophasic" action potentials. By altering one or both at will, a variety of abnormal electrocardiograms may be constructed (fig. 55). This *interference theory* is based primarily on experimental records where one electrode is placed on intact heart muscle or even on the thoracic cage, while the other rests on a section of muscle that has been injured. It is assumed that the resulting record reflects the potential variations of the uninjured region exclusively and that the electrode resting over the injured muscle may be considered a neutral reference point. This is in serious conflict with the known behavior of tis-

sues when submerged in an extensive conducting medium where no point on the activated structure can be regarded as indifferent. Monophasic curves obtained by this technic actually express the difference in potential between the inside of the cell (injured region) and the outside of the cell (uninjured region), and they are directly com-

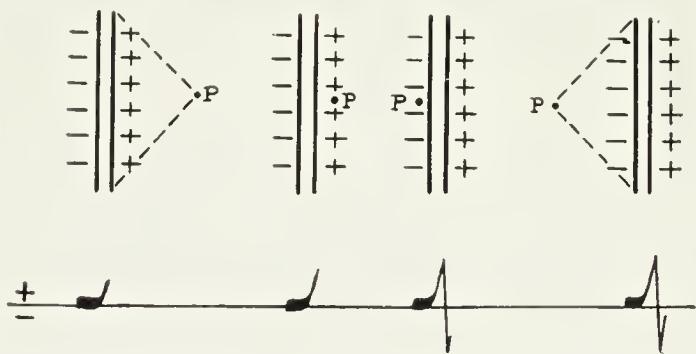


FIG. 54. The dipolar concept of cardiac action currents and the intrinsic deflection.

P defines a point representing the location of the exploring electrode. Electrical potentials recorded at P will show increasing positivity as the action current advances in the direction of P. As the dipole passes over P, the potentials at this point will swing from maximum positivity to maximum negativity and the distance between the peaks will be proportional to the width of the dipolar band of cardiac accession. The interconnecting line between the two maxima of the curve is closely related though perhaps not identical with Lewis' intrinsic deflection. (Courtesy, Hecht and Woodbury: *Am. Heart J.*, 1950.)

parable to monophasic recordings from nerve. The theory is mentioned because it has found widespread acceptance and has certain conveniences. It has little resemblance to reality.

A more detailed inspection of the basic plus-minus deflection obtained during activation of atrial tissue (figs. 53, 54) will reveal other interesting facts. This distance between the two maxima of the curve, when recorded directly from muscle, should represent the effective source-sink distance which, in the mammalian heart, apparently lies in the neighborhood of 5 to 10 mm. The interconnecting line of the recorded image between the two maxima represents an integral part of any curve recorded in the manner outlined. It has therefore been termed the *intrinsic deflection* by Lewis, Meakins, and White. It is apparent that the onset of the intrinsic deflection (the maximum positive peak of the curve) signals the arrival of the excitation at the region in contact with the electrode (fig. 54). Comparing the onset of the intrinsic deflection of various

atrial regions, the velocity of transmission of activity through mammalian atrial muscle has been estimated to approximate 0.15 to 1 m./sec. The onset of the intrinsic deflection naturally occurs earlier in regions near the pacemaker than

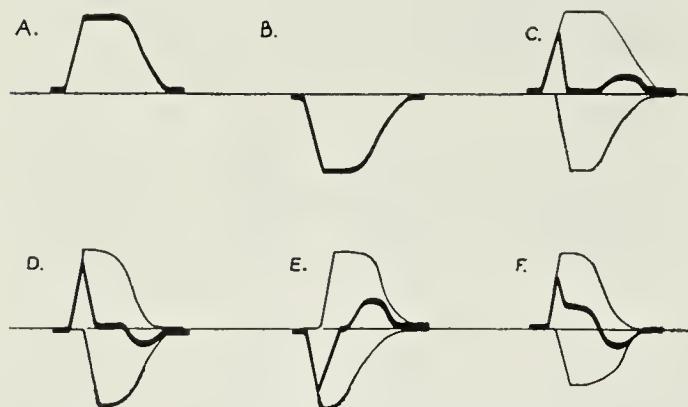


FIG. 55. The interference theory of the electrocardiogram.

The electrocardiogram is considered as the algebraic sum of two "monophasic" components (A and B) which differ from each other in direction and in duration and are slightly asynchronous. The monophasic components are said to express the electrical effects of apex and base, right and left ventricle, or any other two halves of cardiac tissue, according to this theory.

A slight delay in onset of activation of one monophasic component with shorter duration of the excitatory state yields upright QRS complexes and T waves (C). Lengthening of the excitatory state of this component equal to or exceeding that of the second component results in inverted T waves (D). By altering onset, shape, and duration of the monophasic curves an infinite variety of electrocardiographic configurations may be plotted (E, F).

As the length of the excitatory state differs in various sections of cardiac muscle and as changes in its duration undoubtedly account for many T wave changes, the theory has a certain limited usefulness. It has had no satisfactory experimental support and has little resemblance to reality.

in distant areas. This is of decided clinical importance in estimating the location of pacemakers as well as in determining the pathways of transmission through atrial and ventricular muscle.

The activation of *ventricular musculature* differs in two important aspects from that of atrial muscle: (1) The impulse is brought to ventricular muscle over a specialized conduction system and is "delivered" almost simultaneously to large endocardial regions; and (2) depolarization cannot be represented as a wavelike spread over a sheet of muscle, but begins at the endocardial surfaces and, in the main, spreads centrifugally from within outward.

A recent controversy over the existence in dog and man of a *bundle of His* with main branches

and finer ramifications (*Purkinje system*) has restimulated a series of reports on painstaking dissections of human embryonic hearts. In the ungulate animals (sheep, cattle) the system is well developed and may easily be discerned with the naked eye. It is poorly differentiated from ordinary cardiac muscle in the adult heart of dog and man. The newer studies confirm the previous concept that strands of specialized tissue, containing large amounts of clear cytoplasm and invariably accompanied by nerve fibers, pass from the lower part of the right atrium (region of Aschoff and Tawara) through the membranous atrioventricular septum, traverse over the top of the interventricular septum, and divide into two main branches, one for the left and one for the right ventricle. The branches divide into finer and finer subdivisions, each strand eventually undergoing gradual end-to-end transition into ordinary cardiac muscle. Anatomic and physiologic considerations suggest that the terminal twigs dip more or less deeply into the ventricular myocardium proper, an assumption which is of significance in the interpretation of ventricular activation. These strands of specialized cells are the ventricular structures first to be activated.

It is uniformly agreed that the endocardial surface is next to be depolarized and that the action current spreads radially outward thereafter. This follows from the fact that an electrode placed in a ventricular cavity of the normal heart will record a negative potential while septum and lateral wall undergo depolarization. An electrode placed over the epicardial surface will record a positive deflection as long as the action current spreads toward this area.<sup>1</sup> With the arrival of the impulse at the region subjacent to the electrode, maximum positivity will be noted (fig. 54). A sudden reversal of polarity (the onset of the intrinsic deflection) signals complete local depolarization. It is obvious that the onset of the intrinsic deflection (in leads not in immediate contact with heart muscle, termed *semi-intrinsic* or *intrinsicoid*) will be earlier over the thin right ventricle (less muscle to traverse), and the initial upstroke (R wave) smaller than over

<sup>1</sup> In general, a positive deflection at the active electrode indicates an approaching wave of excitation while a negative deflection indicates a receding wave of excitation (see figure 54).

the left (fig. 56). In normal hearts the difference between the two deflections approximates 0.02 second. In ventricular hypertrophy these differences in the activation of the respective epicardial surfaces are either accentuated (left

## THE INTRINSIC DEFLECTION

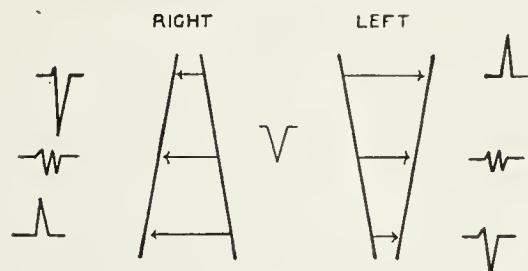


FIG. 56. Extrinsic and intrinsic influences upon the electrocardiographic pattern in direct and semidirect leads.

Thin ventricular muscle will give rise to small R waves, early intrinsic deflections, and big S waves (upper left-hand section and lower right-hand section). Thick ventricular layers are characterized by large upright complexes and late intrinsic deflections (upper right-hand section and lower left-hand section).

The remote effects of distant areas will impress itself upon the exploring electrode because, after the impulse has invaded the subjacent tissues, other regions are still undergoing active depolarization. The upper section of the diagram illustrates the right and left ventricular activation in a normal heart and in examples of left ventricular enlargement. The lower section depicts the characteristic pattern over right and left ventricle in right ventricular hypertrophy. The centrifugally spreading impulses of the normal or of the hypertrophied heart will leave the ventricular cavities in the wake of the action current, and endocardial electrocardiograms are therefore always predominantly negative (center tracing).

ventricular enlargement) or reversed (right ventricular enlargement) (fig. 57).

It must be remembered that the recording electrode depicts the potential variations of the subjacent region with respect to cardiac activation as a whole. The entire ventricle considered as a hollow shell is activated almost simultaneously and an electrode placed over a region that has not yet or has already been depolarized records potential changes as long as other remote regions are being invaded by the action current. The deep downward stroke over the right ventricle is an example of the effect of cardiac activation of remote areas (figs. 56, 57).

In many instances the anterior portion of the left side of the interventricular septum is the first portion to be invaded. For a brief initial period the impulse spreads from left to right in

many, though not in all, instances: an electrode over the lateral wall of the left ventricle describes an initial negative period, and an electrode within the right ventricular cavity describes a small initial positive deflection (fig. 58). This peculiar

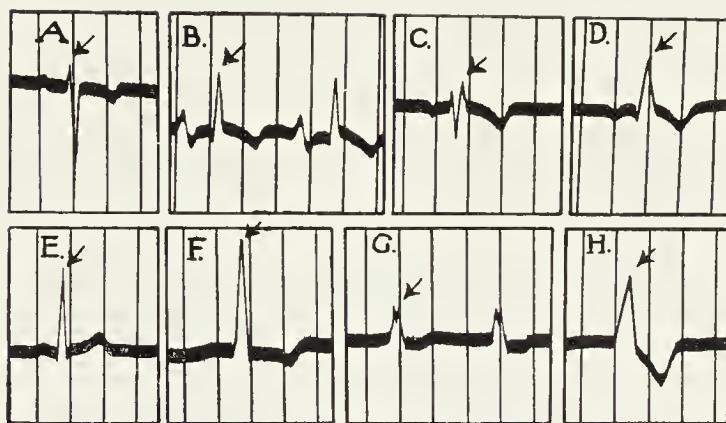


FIG. 57. The intrinsicoid deflection of the precordial electrocardiogram.

A to D are records obtained from  $V_1$  and illustrate the effects of changes in activation of the right ventricle. E to H were obtained from  $V_6$  (left ventricular pattern). A and E show a normal heart with early intrinsicoid deflections. The later onset of the downstroke of R and the greater height of the "pre-intrinsicoid deflection" (rising limb of R) over the left ventricle are occasioned by the greater muscular mass to be traversed by the action current when compared to the right. B and F are instances of right and left ventricular enlargement respectively. The biphasic P in B indicates left auricular enlargement. Slurring and widening of QRS in  $V_6$  denotes slight delay in intraventricular conduction presumably caused by excessive cardiac dilatation which was present in this case. C and G are instances of incomplete, and D and H of complete, right and left bundle branch block with marked delay in the onset of the intrinsicoid deflection. Arrows point to the onset of the intrinsicoid deflection. Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec. (Compare to figure 56.) (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

and clinically insignificant behavior explains the *normal Q wave* of ventricular leads or of leads in which the effects of this chamber are being recorded (lead I,  $V_L$  or  $V_F$ ,  $V_5$ ,  $V_6$ ).

The details of ventricular activation of the normal heart may vary from subject to subject. It suffices to state that in the normal heart specialized tissue is first involved in depolarization, the apical regions of the subendocardium and the anterior portion of the interventricular septum next, the lateral ventricular walls later, and the posterolateral left ventricular wall and the right ventricular conus region last.

Abnormal ventricular excitation occurs when

either one of the branches of the conduction system fails (*bundle branch block*) or when a new impulse center arises in one of the ventricles (*extrasystoles, idioventricular centers* in complete A.V. block). In bundle branch block the unin-

lated positive peak. In other words, the onset of the intrinsic deflection is strikingly delayed (fig. 54). This constitutes the only reliable sign of bundle branch block (see below). In ventricular extrasystoles and idioventricular rhythms similar considerations apply, but, due to the many variations possible in the location of the new pacemaker, the detailed interpretation is of necessity more complicated.

Ventricular activation is also altered in instances of ventricular dilatation and hypertrophy (*ventricular enlargement*). Although the order of excitation remains unchanged, the delay in reaching the epicardial surfaces occasioned by the increased muscular mass may readily be demonstrated from estimating the onset of the intrinsic (or intrinsieoid) deflection. An increase in the height of the main ventricular deflection usually noted over the involved ventricle is explained, at least in part, by the delay in the downstroke of the curve and thus correlates with the increase in muscular mass (fig. 57). This is almost always true for predominant left ventricular enlargement. In right ventricular hypertrophy the summed effects of the septum, left ventricle, and perhaps of papillary muscle occasionally tend to obscure the two cardinal signs of ventricular enlargement: increase in R and delay of intrinsic deflection.

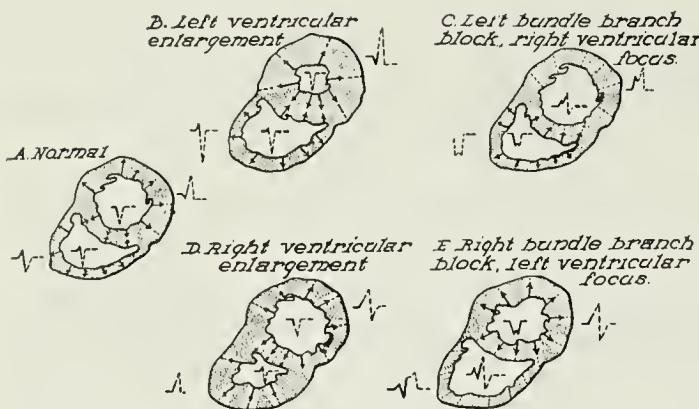


FIG. 58. The order of ventricular excitation in the normal heart, in ventricular enlargement, and in bundle branch block.

The arrows indicate the direction of invasion of ventricular muscle at a time corresponding to about 0.05 second after the beginning of ventricular excitation. Assuming dipolar excitation, the heads of the arrows are electropositive, the tails electronegative. Subendocardial Purkinje fibers and their terminal twigs are indicated by a black line. The heavy tracings indicate the state of activation and the electrocardiograms resulting therefrom at the time interval of the diagram. The dotted lines and thin outlines indicate the later stages of activation. Detailed configuration of right and left ventricular enlargement and of right and left bundle branch block have been accurately drawn. It may be seen, for instance, how the first component of QRS in right bundle branch block over the precordium is a simple reflection of the endocardial pattern and that only the final part of the splintered curve may be considered caused by activation of regions actually underlying the electrode. Similar deductions may be made for the other types of examples.

All illustrated patterns have been obtained from the human heart *in situ* by the use of semidirect precordial, esophageal, and endocardial leads.

involved ventricle is, of course, normally depolarized. The contralateral ventricle is activated from the normal side via the septum. Conduction velocity in ventricular muscle is slow, and a delay in activation of both endocardial and epicardial surfaces of the involved ventricle is readily noted. Records obtained from the cavity of the involved ventricle reveal a positive deflection as long as the action current spreads toward this ventricle, because during this period the electrode faces the positive head-on side of the dipole. The epicardial region of the involved side at first remains quiescent, and an electrode placed upon it records the endocardial pattern. As the lateral wall is finally invaded, the record rises to a be-

A peculiar condition is occasionally encountered in which an *anomalous atrioventricular excitation* occurs due to the existence of conducting strands in addition to the regular pathways. The accessory bundle or bundles carry activation prematurely to some regions of ventricular muscle which then respond in advance of the regular process that activates the remainder of the ventricular musculature. This phenomenon of *pre-excitation* of certain parts of ventricular muscle yields characteristic curves. The QRS complexes appear prolonged and begin almost immediately after the preceding atrial complex. The resulting electrocardiograms therefore demonstrate an apparently short PR interval and a wide QRS complex (*Wolff-Parkinson-White syndrome*). Double conduction of this sort does not impair cardiac efficiency, although these patients are often subject to paroxysmal auricular tachycardia or auricular fibrillation presumably on a re-entrant basis.

**Nature and Spread of Repolarization: Recovery Phase.** The return of activated cardiac muscle to its diastolic resting stage results in electrical events that are characterized by a slow deflection, usually four or five times as long and generally not more than one third as large as the excitation deflection. The interpretation of events leading to recovery is obviously concerned with repolarization. The details rest on much more tenuous grounds than the comparatively clear-cut concepts regarding the depolarization process. If excitation has been likened to a band of dipoles with a layer of positive charges immediately followed by a layer of negative charges and spreading in one direction over cardiac muscle, recovery may be expressed by a moving dipole with negative charges followed by positive ones and presumably spreading in the opposite direction. The width of the dipole is greatly increased, however, and therefore a sharp intrinsic deflection is not obtained. In consequence, one of the valuable tools for the study of excitation is not available for the study of repolarization.

It is obvious that the spread of excitation and the order of invasion (QRS) to some extent influence spread and order of recovery (T), and that the two processes are closely interdependent. The geometric and mathematical relationship of this interdependence is also determined to some extent by the placement of the electrodes with respect to the source of the current. Detailed considerations of all these factors with regard to repolarization and its application to the clinical interpretation of the slow deflection (T wave) of the electrocardiogram is therefore relegated to later sections of this chapter. Some general statements may be made, however. The deflection of the electrocardiogram which represents repolarization (the T wave) may be altered (1) if the *direction* from which repolarization occurs is changed and (2) if the *rate* at which certain sections return to the resting state is modified, or, in other words, if the length of the excitatory state of individual muscle units is abbreviated or unduly prolonged when compared to other regions of cardiac muscle.

The former serves to explain alterations of the recovery deflection when, in an otherwise normal heart, the spread of the impulse and with it the order of excitation is suddenly changed. Of necessity, the *direction of repolarization* is like-

wise altered. This explains the striking changes of the T wave in extrasystoles (fig. 46), aberrant ventricular complexes (fig. 49), bundle branch block (fig. 57), and certain idioventricular rhythms arising distal to the branching of the bundle. These changes in T wave do not, by themselves, indicate myocardial disease. Changes in the *rate of repolarization*, on the other hand, may occur independently of direction and of spread of excitation. This results in modification of the recovery deflection (the T wave) independent of changes of the excitation deflection (QRS group). The rate of recovery and the length of the activated state differ from region to region, even in the normal heart. Further changes resulting in excessive local *repolarization delay* may be induced by many physiologic procedures, by drugs, and by abnormal pathologic states. The interference theory mentioned above can neatly account for these changes by assuming that the duration of one of the two monophasic components is altered—which is another way of stating that local changes in the length of the activated state cause modifications in the recovery deflection (fig. 55). If the delay is not excessive, complete repolarization does take place and the entire muscle will return to a fully polarized resting stage during the diastolic period. Local differences disappear at rest.

If, however, the local delay in repolarization is excessive, it may carry into diastole, and these regions will fail to become completely repolarized. They will remain electrically negative when compared to the rest of cardiac muscle. This *flow of resting current* is very similar, though not identical, to the "injury current" observed in nerve and muscle, and will impress itself upon the electrocardiographic record as a displacement of the segment of the record which links excitation deflection with recovery deflection (RST junction). The direction of the displacement is primarily dependent on the location of the observing electrode with respect to the "injured" region. This is illustrated in figure 59.

Shifts of the RST segment may also occur if the region "injured" recovers completely during diastole but fails to become completely depolarized during systole (locked polarization). Potential difference would then be present at the height of activation (injury current of activity). This concept is less well established than the conventional one illustrated in figure 59. It is possible

that both failure of complete polarization and failure of complete repolarization may contribute to the familiar clinical pattern of RST segment shifts.

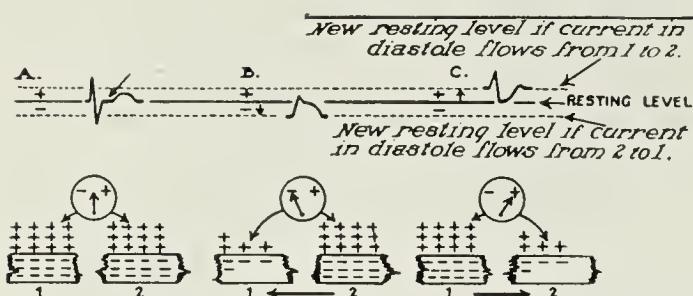


FIG. 59. Displacement of the RST segment. The RST junction (arrow in A) may be displaced either upward (B) or downward (C), depending on the location of the observing electrodes with respect to the "injured" region responsible.

In A (normal), complete repolarization of all muscle units occurs at rest and therefore no potential differences exist between any of the muscle units, and the recording galvanometer returns to the resting level. In B, one segment (region 1) fails to undergo complete repolarization at rest, and therefore at rest a current will flow between sections 2 and 1. It causes negative displacement of the recording string (new resting level, with galvanometer registering negativity) except when complete depolarization occurs at the height of systole where no current flows between any regions. The galvanometer will return briefly to the true resting level. The difference between this and the new diastolic resting level (arrow in B and C) is directly proportional to the height of the current flowing in diastole. In C, the situation is similar to B except that either the recording electrodes have been placed differently, or other regions have been involved. The current now flows from 1 to 2 and the new resting level of the galvanometer will be on the positive side of the original base line. It may be noted that there are no fundamental differences between upward and downward displacement of the RST junction.

#### SPREAD OF CURRENT THROUGH BODY TISSUE. ELECTROCARDIOGRAPHIC LEADS

Having dealt with the general aspects of electrical responses of tissues and with the application of these principles to the heart muscle, it becomes necessary to discuss modifications which are dependent on the placement of the electrodes upon the body. The various recording systems now in use are interdependent, and an intimate relationship may be demonstrated to exist between electrocardiograms obtained by leading directly from the surfaces of the exposed heart (direct leads), from the vicinity of cardiac muscle (precordial and esophageal leads), and from the periphery of the electric field (unipolar and bipolar limb leads).

**Spread of Current Through Body.** An excitable tissue such as the heart may be considered to be an active center from which electrical events spread toward the periphery. The body, through which these currents flow, may be considered an electrolyte medium which passively conducts electricity according to the principles of electrical conduction in volume conductors (see p. 346). Differences in conductivity of various body tissues (lungs, bones) may be neglected. Upon reaching the body surface, the potential variations may be recorded by suitable electrode arrangements.

Assuming passive conduction between heart and skin, the potential variations observed at the surface of the body will change in unison with that of the heart muscle and according to the laws of volume conduction as discussed above. The changes in electrical potential of different regions of the heart are transmitted to different areas of the body so that the potential variations recorded from certain zones of the body surface differ from each other. Comparing the pattern that one obtains from various points on the body surface with that obtained by directly leading from the different regions of the heart, one may clearly discern that (1) the straight anterior portions of the right ventricle appear on the anterior thoracic wall; (2) the left lateral cardiac regions appear on the left side of the chest and left shoulder; (3) the diaphragmatic surfaces appear on the lower part of the trunk; (4) the posterior ventricular segments appear over the left axillary line, the lower esophagus, and the back; (5) the effect of the cardiac base and endocardial cardiac surfaces (by means of the large vascular openings at the base) appear on the right upper chest and right shoulder; (6) the left atrial regions and left ventricular endocardial segments appear on high esophageal regions (see table 35).

In the electrical sense the extremities may be considered as simple extensions of the regions of the trunk to which they are joined, so that the left arm represents changes identical to those obtained from the left upper chest and shoulder; the right arm, those from the corresponding regions on the right; and both legs, those from the lower part of the trunk (fig. 60).

**Electrocardiographic Leads.** Electrocardiographic connections are made with the body between the two terminals of the recording galvanometer. It is important to realize that any

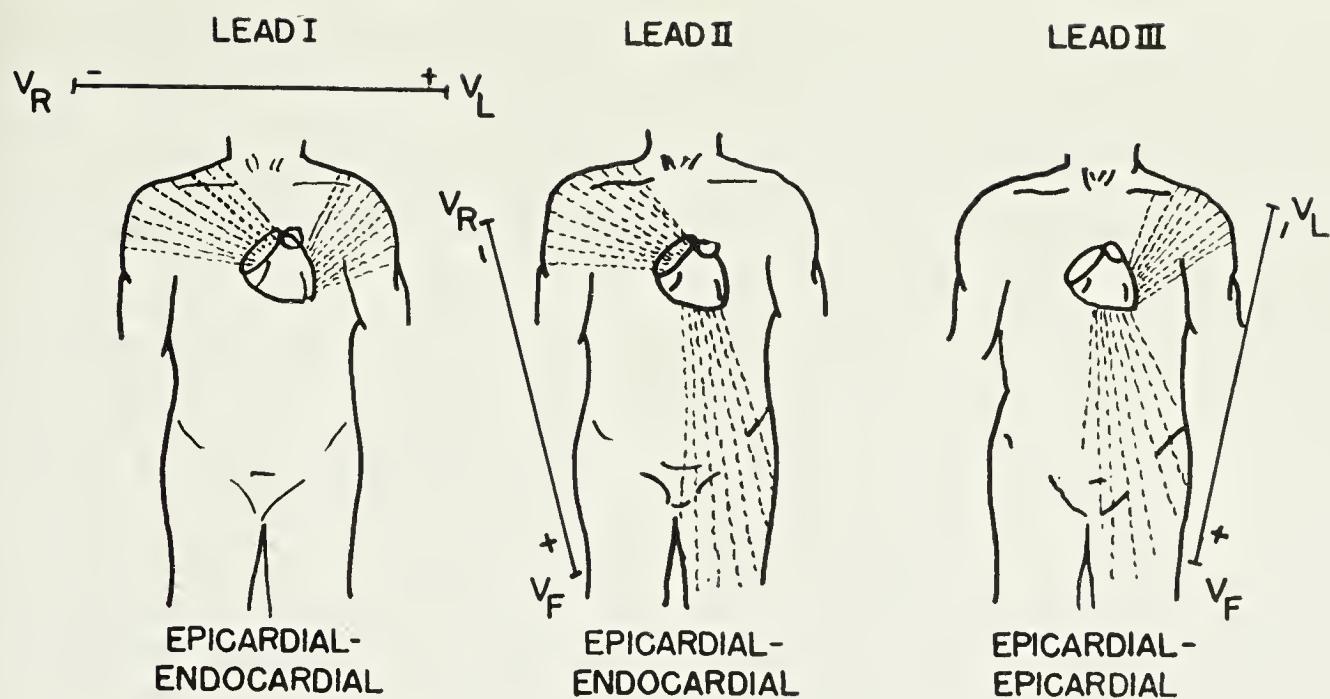


FIG. 60. The standard bipolar limb leads. The potential variations of the heart may be recorded by placing electrodes on the extremities. The electrical events of certain sections of the heart influence the changes in electrical potentials of an extremity to a greater degree than those of others, and areas perpendicular to the plane of the extremities contribute little if anything to the standard limb leads. See text and table 35. (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

electrocardiogram represents the algebraic summation of the electromotive forces recorded by two electrodes which have been placed on two different positions of the body surface. If both recording electrodes are so placed as to be nearly equidistant from the source of the action current, they will contribute equally to the resulting electrocardiogram (*bipolar leads*). If one electrode (exploring electrode) is placed close to the source of the current (chest wall, esophagus, endocardium) and the other distant from it (distant or indifferent electrode), size and shape of the galvanometric deflection is then largely determined by the potential variations occurring underneath the exploring contact (*unipolar leads*). Electrocardiographic connections (leads)

are termed *direct* and *semidirect* if at least one electrode is placed in contact with, or in the vicinity of, cardiac muscle. They are termed *indirect* if all electrodes are distant from the source of the current. The various combinations of leads and terminologic possibilities are enumerated in table 34.

In unipolar leads the potential variations of the distant electrode are to be kept at a minimum if the resulting record is to represent a true image of the changes occurring underneath the exploring contact.

The zero line of the voltage distribution in a volume conductor can serve as a reference for measuring the voltages (see I in figure 44). Any

Table 34  
ELECTROCARDIOGRAPHIC LEADS\*

	<i>Direct</i>	<i>Semidirect</i>	<i>Indirect</i>
Unipolar.....	Leads from cardiac surfaces	<i>Precordial and thoracic leads, esophageal leads, endocardial leads</i>	<i>Limb leads V<sub>R</sub>, V<sub>L</sub>, V<sub>F</sub></i>
Bipolar.....	Leads from cardiac surface using differential electrodes	(Thoracic or esophageal leads with two exploring contacts)	<i>Standard limb leads I, II, III</i>

\* Leads most commonly used are italicized.

electrode placed a great distance from the source and the sink will lie approximately on or close to this zero line. Thus for the recording of the electrical field about a source and sink in a volume conductor, any sufficiently remote electrode will serve as an indifferent electrode. With the action current traversing a large area of cardiac muscle, however, no single point of the body surface remains uninfluenced by the electrical events of excitation and recovery, and no one position may be considered at zero potential throughout the cardiac cycle. It is therefore obvious that the distant electrode, when placed on any one point of the body, may exert a more or less considerable influence upon the final record, depending on the size and intensity of the potential variations of the region upon which the "indifferent" electrode has been placed. The difficulties can largely be avoided if the exploring electrode is paired with an artificial ground, a neutral electrode introduced by Wilson and his co-workers. This consists of three wires. One end of each wire is connected to electrodes placed on the left arm, the right leg, and the left leg (positions used for the recording of standard limb leads); and the other ends of the wires are soldered together to form the center of a tripod (*central terminal*). The central terminal is connected to one end of the galvanometer, the exploring electrode to the other. It appears likely, on theoretic grounds, that the central terminal undergoes no appreciable changes in electrical potential throughout the cardiac cycle. In terms of the volume conductor theory the central terminal may be considered to lie in the field of the weak outermost isopotential lines of figure 44. This places the central terminal more firmly on the isoelectric line I.

Small 5000-ohm resistances are usually placed in the circuit of the neutral electrode, between one extremity and the central point, thus increasing the over-all resistance from one extremity to the other to 10,000 ohms. The resistors are not essential to the system, especially if amplifier type electrocardiographs are employed.

This "artificial ground" is preferred when semidirect leads are to be recorded. If only one point on the body surface is chosen for the position of the distant electrode, the right side of the back may be used because, in most instances, the potential variations of this area appear to vary through a relatively small range. If one extremity is to be used, the distant electrode should be

placed upon the right arm because the potential variations of this region remain relatively uniform from case to case. There is little excuse for placing the "indifferent" electrode upon the left arm or the left leg, as the potential variations of these regions change greatly with the position of the heart within the chest.

The standardization of electrocardiographic nomenclature requires that the letter V (a symbol for potential variation) be used whenever the exploring electrode is paired with Wilson's central terminal. Subscripts indicate the position of the exploring electrode (examples:  $V_5$ —unipolar lead from fifth standard precordial position;  $V_L$ —unipolar lead from the left arm;  $VE_{35}$ —unipolar lead from the esophagus with tip of esophageal lead 35 cm. from the front teeth). If the distant electrode is placed on an extremity or over the back, the letters R, L, F, and B are to be used (examples:  $CR_5$ —chest leads with distant electrode on the right arm, exploring electrode at fifth standard precordial position;  $EF_{50}$ —esophageal lead, distant electrode placed on the left leg, tip of esophageal lead 50 cm. from the front teeth).

Over the years, there has evolved for practical use a system combining a series of bipolar leads and a number of unipolar leads that allows a reasonably complete estimation of the electrical events occurring with the heart beat, and that provides information on the spatial position of the heart and its various electrical subsections. *Three standard bipolar limb leads* (I, II, and III) have been in use for many years and provide the basis for any electrocardiographic examination by demonstrating the over-all electrical events of large areas. They are supplemented by *unipolar semidirect leads* (from the precordium and esophagus) which allow detailed information of relatively small sections of cardiac musculature and may be directly compared with direct leads taken from cardiac muscle, which they closely resemble. To these are often added *unipolar limb leads* ( $V_R$ ,  $V_L$ ,  $V_F$ ) obtained from the three extremities which combine to yield standard bipolar leads (fig. 60). Not all these leads need be recorded on every patient, and the selection of leads to be obtained depends primarily on the clinical problem at hand. At times it may be necessary to explore the patient with as many as 30 different leads or more; on other occasions the

use of a single standard limb lead or a precordial lead may be sufficient to provide the information desired.

*Bipolar limb leads* (the standard leads I, II, and III) yield electrocardiograms obtained by using a recording system in which both electrodes are placed equidistant from the heart. The size and shape of the record are determined to an equal degree by potential variations occurring underneath the two electrodes. Of the many possible combinations, Einthoven suggested that the electrodes be placed upon three extremities and that three connections be used which are so interrelated that one extremity is common to two connections (fig. 60). Standard bipolar limb leads therefore represent the algebraic summation of the electromotive forces transmitted to two extremities. With reference to a conventional system by which an upward deflection indicates positivity, the standard leads may be further defined:

Lead I: Left arm and right arm electrode connected to the galvanometer. Positivity of the left arm is represented by an upward deflection of the electrocardiogram ( $I = V_L - V_R$ ).

Lead II: Left leg and right arm electrodes connected to the galvanometer. Positivity of the left leg is represented by an upward deflection of the electrocardiogram ( $II = V_F - V_R$ ).

Lead III: Left leg and left arm electrodes connected to the galvanometer. Positivity of the left leg is represented by an upward deflection of the electrocardiogram ( $III = V_F - V_L$ ).

Figure 60 demonstrates that lead I represents the variations in electrical potential to the lateral cardiac wall minus those of the atrial and ventricular cavities; lead II, those of the diaphragmatic surface minus those of the cavities; and lead III, the algebraic summation of the left lateral and the diaphragmatic epicardial surfaces. Regions at right angles to the extremities (straight anterior and straight posterior sections of cardiac muscle) do not usually influence the standard lead electrocardiogram (*silent regions*) (the posterior cardiac surfaces may be considered a "silent" region only if the heart is vertically placed).

*Unipolar limb leads* yield electrocardiograms obtained by using a recording system in which the exploring electrode is placed in turn over one of the three extremities used for the recording of

standard limb leads while the other is connected to the central terminal. Records are obtained from the right arm ( $V_R$ ), left arm ( $V_L$ ), and left leg ( $V_F$ ). They are essentially unipolar and therefore comparable to semidirect precordial or esophageal leads, which they closely resemble. They demonstrate the potential variation occurring at the apices of a triangle formed by the two shoulders and the pubic region which forms the basis for the bipolar standard limb leads. Without introducing large errors, unipolar limb leads may therefore be regarded as the constituents of the three standard bipolar leads. They illustrate the relationship which exists between the standard bipolar limb leads and the unipolar semidirect leads. As the latter are faithful reproductions of the potential variations occurring at the endocardial and epicardial surfaces of the heart, the unipolar limb leads reveal the role that sections of the cardiac muscle play in the formation of the standard limb leads (table 35).

Table 35

AN ELECTROCARDIOGRAPHIC SYSTEM WHICH PROVIDES A SELECTIVE EXPLORATION OF THE HEART MUSCLE

Lead	Significance
I, II.....	Reference leads: endocardial-epicardial summation
III.....	Reference lead: epicardial-epicardial summation
$V_R$ .....	Endocardial ventricular surfaces (right and left)
$V_1$ .....	Atrial surface effect and as $V_2$
$V_2, V_3$ .....	Anterior epicardial surface of right ventricle ("silent" region)
$V_5, V_6$ .....	Low anterolateral and posterolateral epicardial surface of left ventricle
$V_L$ .....	High lateral epicardial surface (left or right ventricle)
$V_F$ .....	Diaphragmatic epicardial surface (left or right ventricle)
$VE_{35-40}$ .....	Left atrial surface, left ventricular cavity
$VE_{45-55}$ .....	Posterior and diaphragmatic surface (left or right ventricle). The pattern is usually, but not always, repeated in $V_F$

It is understood that any lead is influenced by the activation of the heart as a whole.

It may be seen from figure 60 and from table 35 that a unipolar lead from the left arm ( $V_L$ ) reflects the potential variation of the left lateral wall; from the left leg ( $V_F$ ), the potential variation of the diaphragmatic cardiac surfaces; and

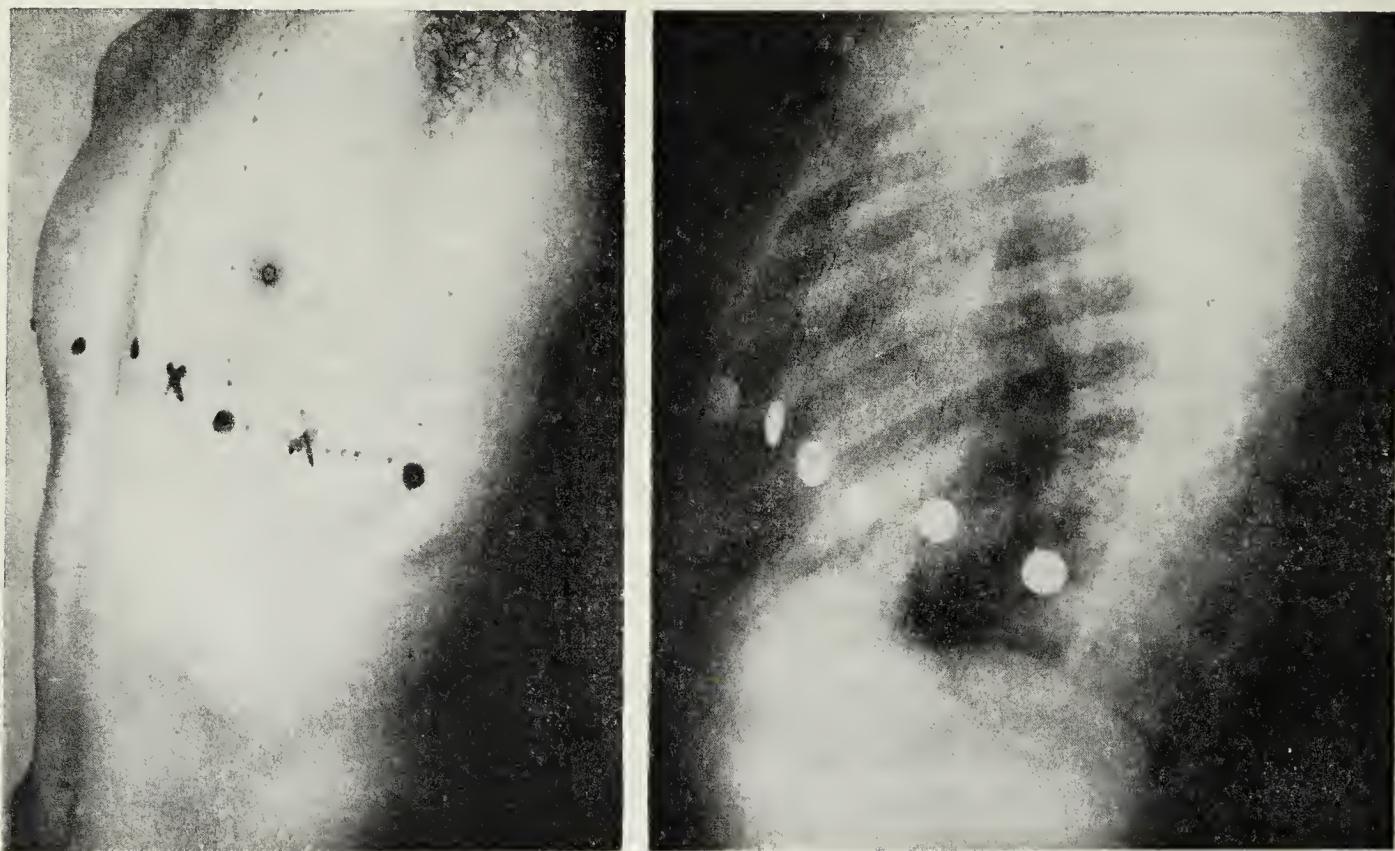


FIG. 61. The standard precordial positions ( $V_1-V_6$ ).  $V_1$ , fourth intercostal space to right of sternum;  $V_2$ , same, to left of sternum;  $V_3$ , between  $V_2$  and  $V_4$ ;  $V_4$ , fifth intercostal space in left midclavicular line;  $V_5$ , between  $V_4$  and  $V_6$ ;  $V_6$ , plane of  $V_4$  in left anterior axillary line. The points may be determined by locating the fourth intercostal space, the midclavicular line, and the midaxillary line. Positions 1, 2, 4, and 6 are easily found; 3 and 5 may be interpolated. Leads over the back are usually taken at the level of positions 4, 5, and 6. An x-ray of the chest reveals the approximate relationships of the precordial position to the cardiae shadow in a normal individual.  $V_6$  is seen to lie posterior to the heart in most radiologic positions.

from the right arm ( $V_R$ ), those of the atrial and ventricular cavities. Rotation of the heart around any of its spatial axes will alter the shape of these leads, particularly  $V_L$  and  $V_F$ , because the regions responsible for their configuration change with the position of the heart within the chest (table 35; fig. 62).

Breaking the connections between the central terminal and the extremity upon which the exploring electrode has been placed results in an increase of the size of the unipolar limb leads by 50 per cent without altering the shape of the curve. For this variant of the unipolar limb leads the term *augmented unipolar limb leads* ( $aV_L$ ,  $aV_R$ ,  $aV_F$ ) has been coined (Goldberger). They possess no fundamental advantage over the conventional records. The resistors should be left in the circuit.

*Unipolar semidirect leads* yield electrocardiograms obtained by using a recording system in which one electrode is placed in close proximity to the heart while the other is far removed from it. The resulting record is in many respects

similar to tracings obtained when the exploring electrode is placed in direct contact with cardiac muscle, and therefore the use of multiple semidirect leads will provide an accurate selective exploration of cardiac muscle. In general, the anterior and lateral surfaces of the heart are best explored by moving the electrode from right to left, beginning at the right sternal border at the approximate level of the cardiae apex (fig. 61). Moving on in the same plane toward the back or encircling the entire chest at the level of the apex is occasionally helpful, as are positions over the pulmonary conus or over the higher lateral regions of the left chest in the axilla. The posterior surface of the heart may be explored by placing the electrode over the back or in the esophagus. The diaphragmatic regions are best explored from lower esophageal positions and occasionally in leads from the ensiform process of the sternum ( $V_s$ ). The potential variations of the ventricular cavities may be recorded if the electrode is placed over the right upper anterior chest wall, the right acromial region, the right

side of the back, or high in the esophagus. Atrial deflection may be studied with the exploring electrode placed at the right side of the lower sternum and in the upper region of the esophagus.

Of the many positions over the thorax, the back, and the esophagus, six *standard unipolar precordial leads* may in the majority of cases be the most helpful adjuvants to the standard bipolar leads. Their position with respect to the landmarks of the chest and to the heart itself may be seen from figure 61 and its legend.

The use of *esophageal leads* is occasionally advisable because it allows for a detailed exploration of atrial and posterior ventricular segments. The former may be of value in certain auricular disorders (fig. 203), the latter in lesions of the posterior surface that may not always be deflected to the left leg. It appears desirable to obtain at least four positions if a complete posterior exploration of the heart muscle is desired; one at the level of the diaphragm, approximately 50 cm. from the front teeth; one strictly posterior, usually at 45 cm.; one intermediate between ventricular and atrial levels (40 to 44 cm.); and one from the immediate vicinity of the left atrial musculature (35 cm. from the front teeth and usually 10 cm. cephalad from the ventricular lead). The atrial component of high esophageal lead reveals a true biphasic pattern with a clear intrinsicoid deflection (fig. 62), the only semidirect lead for atrial muscle other than those obtained by blood contact (endocardial leads). The ventricular component of high esophageal leads reflects primarily the potential variations of the left ventricular cavity. In contrast to precordial leads, lower ventricular esophageal leads are profoundly influenced by the position of the heart within the chest, and in this respect behave similarly to V<sub>F</sub>.

In cases of unusual cardiac rotation or extraordinary order of excitation, *circumferential unipolar thoracic leads* may be helpful. They encircle the back at the level of V<sub>6</sub> and merge into precordial leads from the right side of the chest similar in location to the points from which standard precordial leads are taken. Leads from the posterior axillary line and to the left of the vertebral column are normally similar to those from the left side of the precordium. The deflections of leads from the right side of the back often resemble V<sub>R</sub>, and those from the right side of the precordium generally resemble V<sub>1</sub>.

## FORM OF NORMAL ELECTROCARDIOGRAM

**Normal Pattern.** Satisfactory statistical data on the normal range of the electrocardiogram are scarce. Approximate data compiled from available figures are listed in tables 36 and 37.

Table 36

DURATION OF ELECTROCARDIOGRAPHIC COMPLEXES\* AND INTERVALS (IN SECONDS)

Terminology	Significance	Duration																																		
P.....	Activation of both atria	0.04-0.12																																		
PR.....	Atrioventricular conduction time	0.12-0.21†																																		
QRS.....	Ventricular excitation	0.06-0.10																																		
QT.....	"Electrical‡ systole"	<table border="1"> <thead> <tr> <th>Heart Rate</th> <th>QT Ranges</th> </tr> </thead> <tbody> <tr> <td>45-50</td> <td>0.40-0.51</td> </tr> <tr> <td>51-55</td> <td>0.38-0.50</td> </tr> <tr> <td>56-60</td> <td>0.36-0.48</td> </tr> <tr> <td>61-65</td> <td>0.35-0.45</td> </tr> <tr> <td>66-70</td> <td>0.34-0.43</td> </tr> <tr> <td>71-75</td> <td>0.33-0.42</td> </tr> <tr> <td>76-80</td> <td>0.32-0.41</td> </tr> <tr> <td>81-85</td> <td>0.31-0.39</td> </tr> <tr> <td>86-90</td> <td>0.29-0.38</td> </tr> <tr> <td>91-95</td> <td>0.29-0.37</td> </tr> <tr> <td>96-100</td> <td>0.29-0.36</td> </tr> <tr> <td>101-105</td> <td>0.28-0.35</td> </tr> <tr> <td>106-110</td> <td>0.29-0.35</td> </tr> <tr> <td>111-115</td> <td>0.29-0.35</td> </tr> <tr> <td>116-120</td> <td>0.27-0.32</td> </tr> <tr> <td>120-150</td> <td>0.25-0.30</td> </tr> </tbody> </table>	Heart Rate	QT Ranges	45-50	0.40-0.51	51-55	0.38-0.50	56-60	0.36-0.48	61-65	0.35-0.45	66-70	0.34-0.43	71-75	0.33-0.42	76-80	0.32-0.41	81-85	0.31-0.39	86-90	0.29-0.38	91-95	0.29-0.37	96-100	0.29-0.36	101-105	0.28-0.35	106-110	0.29-0.35	111-115	0.29-0.35	116-120	0.27-0.32	120-150	0.25-0.30
Heart Rate	QT Ranges																																			
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120-150	0.25-0.30																																			

\* These values are approximate. All depend on the age of the subject (increasing values with advancing age) and on the heart rate (see text). All are based on measurements of standard bipolar limb leads and do not necessarily apply to unipolar limb and pectoral leads. In the latter, slightly longer intervals are not uncommon.

† In heart rates over 100 beats per minute, PR should not exceed 0.19 second. In children up to the age of 13, a PR interval of 0.16 second is considered the upper normal range and, except in slower heart rates, PR should not exceed 0.17 second in subjects up to the age of 17.

‡ Many formulas have been proposed which relate QT to cardiac rate. One commonly used has been devised by Bazett for the mechanical systole:

$$K = \frac{QT \text{ interval}}{R-R \text{ interval}}, \quad K = 0.37 \text{ in males}, 0.40 \text{ in females.}$$

The value is inaccurate.

If one defines a "normal" electrocardiogram as the most common pattern encountered in healthy subjects, fasting, at rest, in the recumbent position, and in apparent autonomic balance, a wide range of variations in shape is ob-

Table 37

## SIZE OF NORMAL ELECTROCARDIOGRAPHIC COMPLEXES (IN .10/mv.)

	Bipolar Standard Limb Leads	Unipolar Limb Leads	Right Ventricular Precordial Leads (V <sub>1</sub> -V <sub>3</sub> )	Left Ventricular Precordial Leads (V <sub>4</sub> -V <sub>6</sub> )	Remarks
PQRS.....	0-2.5	..	1-2	0.5-2.5	..
QRS.....	3-23	0.5-13	7-55	6-52	In V <sub>1</sub> and V <sub>5</sub> and in V <sub>6</sub> QRS does not exceed 30 mv
Q.....	0-3 (0.40)	0-7.6	0	0-3.5	Q in V <sub>R</sub> may measure up to 3 mv. A small Q may occasionally occur in V <sub>3</sub> if a large R is present
R.....	1-23	0-13	1-55.0*	2-46*	In V <sub>5</sub> and V <sub>6</sub> R does not normally exceed 20 mv
S.....	0-6.5	0-10.5	3-39.0*	0-16	..
T.....	-2-+8	-3-+3	-4-+12	2-11	Inversion of T in V <sub>2</sub> is rarely encountered, and in V <sub>3</sub> is never present in normal adult subjects

The statistical material upon which these figures are based in part was obtained by:

\* C. E. Kossmann and F. C. Johnston: *Am. Heart J.*, **10**:925, 1935.

G. B. Myers, H. A. Klein, B. E. Stofer, and T. Hiratzka: *Am. Heart J.*, **34**:785, 1947.

\* J. Nyboor: *Proc. A. Life Insur. Med. Dir.*, 1947.

C. B. Stewart and G. W. Manning: *Am. Heart J.*, **27**:502, 1944.

tained. The form of the electrocardiogram depends on:

1. the internal structure of the heart,
2. the position of the heart within the chest, and
3. the position of the recording electrodes.

The individual architecture of the heart and of its conduction system (1) is responsible for the variety and combinations of deflections that are seen in any one lead. It determines to a large extent the individuality and constancy of the electrocardiograms of most normal subjects. The influence of the spatial position of the heart within the chest (2) upon bipolar and unipolar electrocardiograms is striking, particularly if the heart is rotated around its longitudinal axis. It needs to be considered in further detail (see p. 367). That the position of the recording electrodes on the body surface (3) determines the electrocardiographic pattern obtained has been mentioned in the previous section. It is illustrated again in figure 62, which represents a complete electrocardiographic examination of a 23-year-old normal male. This confusing multiplicity of various electrocardiographic patterns obtained from different electrode positions is greatly simplified if one recognizes the three

fundamental patterns of the ventricular deflections that emerge from the analysis attempted in the preceding pages. All ventricular electrocardiograms, regardless of technic, represent in pure form or in mixtures:

1. the electrical effects obtained by an electrode adjacent to the epicardial surface of the right ventricle;
2. those obtained by an electrode adjacent to the epicardial surface of the left ventricle; and
3. the endocardial pattern. A study of figures 56, 58, and 62 reveals that these simple basic patterns constantly recur in direct leads, in semidirect leads and in unipolar and bipolar limb leads. Their recognition obviates the necessity of memorizing complicated electrocardiographic configurations.

The great variety of contour is accompanied, however, by an orderly sequence of electrocardiographic events. This appears uniform in all species and depends on spread and distribution of cardiac excitation and recovery. It correlates with mechanical events of the cardiac cycle (fig. 47), and may be divided into evidence of atrial and ventricular activation and recovery. It is evident from figure 47 that the onset of

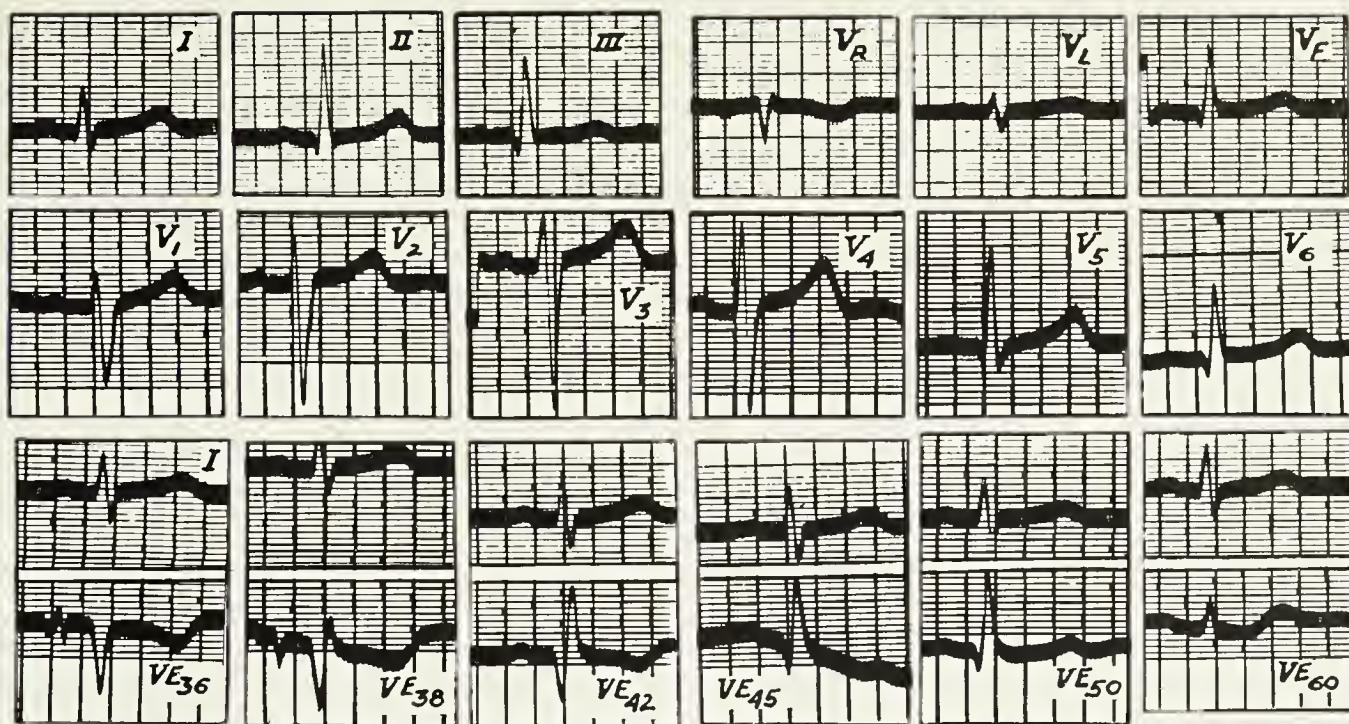


FIG. 62. A normal electrocardiogram. A record obtained from a healthy 23-year-old male subject. The heart appears vertically placed. In the third row, lead I has been recorded simultaneously with esophageal leads. Note the similarity between  $V_R$  and high esophageal leads; between  $V_L$  and precordial leads  $V_1-V_3$ ; and between  $V_F$ ,  $V_6$ , and ventricular esophageal leads ( $VE_{45-50}$ ). Time lines: 0.1 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

electrical excitation always precedes, and recovery coincides with, systolic contraction. The end of ventricular systole occurs simultaneously with the end of electrical activity of the normal, but not necessarily of the abnormal, heart.

The recognizable components of the electrocardiogram in any lead are labeled by the letters O, P, Q, R, S, T, and U. A few general statements concerning the clinically important deflections and intervals, in addition to tables 36 and 37, are given to serve as a guide in the interpretation of clinical records.

**P WAVE.** The P wave represents the electrical effects of atrial excitation. It does not exceed 0.12 second in length in any lead. It is usually slightly notched at its summit. In the normal heart P is always upright in lead I and in all standard precordial leads except  $V_1$ , where at times it shows a small terminal negative component ("biphasic plus minus" P wave). It is always inverted in  $V_R$ . P<sub>T</sub> is rarely seen, but often accounts for a slight depression of the PR segment which is generally slightly below the level of the TP segment.

**QRS GROUP.** Q, R, and S are attributed to the excitation of ventricular muscle. The deflection likewise does not exceed 0.12 second in width. Shape and direction of QRS vary greatly in standard bipolar and in unipolar limb leads, ex-

cept in  $V_R$  where a predominantly downward QRS is the rule (endocardial pattern). Over the right ventricle ( $V_1$  to  $V_3$ ) QRS displays a small R and a deep S wave; over the left ( $V_5$  and  $V_6$ ), a large R wave is often preceded by a small Q (figs. 56, 57, 58, 62). The transition from the right to the left ventricular pattern occurs usually in precordial leads between  $V_3$  and  $V_5$  (fig. 62).

For the purpose of description, the individual components of the excitation deflection are always identified as follows: The earliest upright deflection is labeled R. Any downward deflection preceding R is termed Q. If the string or beam overshoots the isoelectric reference level upon its return from the summit R, a negative deflection is recorded which is termed S. The first of any upward deflection following S is labeled R', the first of any downward deflection following R is called S', and so forth for R'', S'', R''', S''''. When R is absent, a single downward deflection is labeled QS.

Even in the normal subject the QRS complex is not always smoothly recorded. Irregularities in contour may appear which are termed "notching," "slurring," or "splintering" of the record.

The increase in the early negative component of QRS, the Q wave, at the expense of R is an

important sign of tissue destruction in myocardial infarction (see p. 380). The normal range of Q is therefore of special interest. No Q wave should ever be present in leads representing the electrical effects of the right ventricle ( $V_1$  to  $V_3$ ,  $V_L$ , or  $V_F$ , respectively). A small Q wave, rarely more than one tenth of the size of the accompanying R and measuring from 0.5 to 3 mv. (depending on the over-all size of QRS), is a normal feature of the precordial electrocardiogram from the left ventricular region (fig. 58) and is also noted in like proportions, but smaller in actual size, in the unipolar limb lead which deflects left ventricular segments ( $V_L$  or  $V_F$ , respectively). In standard limb leads, Q may be considered a normal variant measuring 0.05 to 0.1 mv., and should not exceed one fourth of the size of the largest deflection in any standard limb lead.

**RT JUNCTION AND RST SEGMENT.** Upon completion of QRS, the string shadow of the electrocardiograph may be found slightly above or below the isoelectric line in any lead. These deviations rarely exceed 0.1 mv. and are of no significance if the voltage of QRS is normal and if the contour of the main section of the T wave is not abnormal. Deviations opposite to the main direction of QRS are the rule rather than the exception in right-sided precordial leads.

**T WAVE.** The final ventricular deflection is influenced by many physiologic as well as pathologic procedures, and may be considered the most labile of all electrocardiographic components. It is termed "flat" if it is lower than the accompanying P wave and "biphasic" if the final component lies on the opposite side of the isoelectric basal level with respect to the RT junction. In a normal heart T is never inverted in lead I or in leads from the left precordial region if the central terminal is used as an indifferent electrode. It is always inverted in leads  $V_R$  and in high esophageal leads (fig. 62). In vertically placed hearts T may normally be inverted in  $V_L$  if the main QRS deflection is downward.

In adults a negative T wave may be encountered in  $V_1$  and occasionally in  $V_2$ . In children inverted T waves in leads  $V_1$  to  $V_3$  are usually noted up to 12 years of age. The "juvenile pattern" may occasionally persist into adolescence or it may have disappeared before the age of 10. Inversion of T waves in  $V_4$  (not in IVF!) and

in left ventricular leads should be viewed with suspicion.

All electrocardiographic deflections are influenced by the heart rate and by the metabolic state of cardiac muscle. The influence is difficult to ascertain in the relatively rapid deflections, but appears striking when the intervals from one deflection to another are measured.

**PR INTERVAL.** This interval, measured from the beginning of P to the beginning of QRS, never exceeds 0.21 second in the normal heart not under the influence of an excessive vagal tone. Short PR intervals are occasionally encountered with an apparently normal sinus mechanism and with normal P waves. Their significance is doubtful. As conduction is extremely slow through the atrioventricular node when compared with the remainder of the conduction system, alterations in PR interval may be taken to indicate primarily a delayed conduction through this structure.

**QT INTERVAL.** This is measured from the beginning of QRS to the end of T and expresses what has been termed the *electrical systole*. It varies with the heart rate. Depending on the cycle length, QT ranges from 0.25 to 0.51 second. A number of formulas have been devised attempting to relate QT to cardiac rate, but it is not generally appreciated that for any given heart rate there exists a relatively wide range of the normal QT interval. In estimating QT intervals it is wise, therefore, to compare the actual values with available tables giving range or upper limits for QT at various cycle lengths (table 36).

**Cardiac Vectors, Area of Electrocardiogram, and Ventricular Gradient.** The electromotive forces waxing and waning during the cardiac cycle may be represented geometrically by a line segment which has length and direction. A force which can be expressed by a line of definite sense and magnitude is termed a *vector*. For any given moment the sum of the electrical effects of activated regions of the heart may be defined by a vector pointing from one region of the heart to another. The vectors will have a certain size and a certain spatial position, and they will vary from moment to moment as the various sections of cardiac muscle become successively activated. These instantaneous vectors were termed by Einthoven the *instantaneous electrical axes* (fig. 65). The mean direction of all electromotive forces during atrial and ventricular excitation

(P<sub>QRS</sub>, QRS) and during atrial and ventricular recovery (P<sub>T</sub>, T) may likewise be expressed as a vectorial force. They may be termed the *modal electrical axes* (figs. 63, 64). They are the vectors most commonly referred to as "electrical axes"

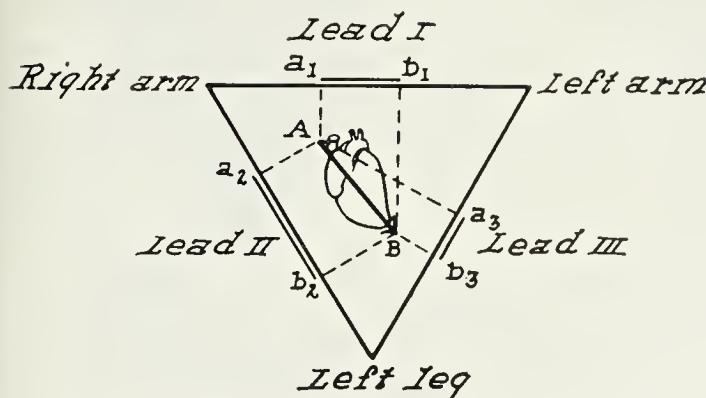


FIG. 63. A cardiac vector and its components. If an electromotive force during the cardiac cycle would have the direction AB when projected on the frontal plane of the body, its components may be plotted as indicated. Knowing at least two of the components (the standard leads), AB, the "manifest potential" of Einthoven may easily be determined geometrically. The body here is considered as a relatively infinite medium with the heart at its center. This approach to estimate the manifest potentials or true (spatial) vectors has always been considered an approximation only.

in clinical electrocardiography, and their components are usually represented by the peaks of the deflections of the electrocardiographic tracings (fig. 64). Lastly, the sum total of all effects throughout the cardiac cycle of either the atrial

or the ventricular events may be represented by a spatial vector. This is obtained by measuring the area of the electrocardiographic deflections rather than their height and direction alone. These vectors represent the *mean electrical axes* of P<sub>QRST</sub> or of QRST. The vector of QRST has been termed the *ventricular gradient* by Wilson.

The projection of a vector on a line is called the *component* of a vector. Any vector may be constructed if two of its components are known. These considerations led Einthoven to adopt the system of bipolar leads which may be considered as representing the components of the vectorial forces of the heart as projected on the frontal plane of the body, which he termed the *manifest potentials* (fig. 63). Since the two legs are at all times at nearly the same potential, and since the extremities upon which the electrodes have been placed simply reflect the potential variations of regions of the trunk to which they are joined, the electrodes may be considered as placed on the apexes of a triangle with the heart at its center. This approximately triangular arrangement of the standard bipolar limb leads provides the basis for two important statements:

1. Knowing the size and direction of two of the vectorial components (two sides of the triangle—two leads), the third component may be constructed from the remaining two (Einthoven's law). This may be expressed otherwise by stating

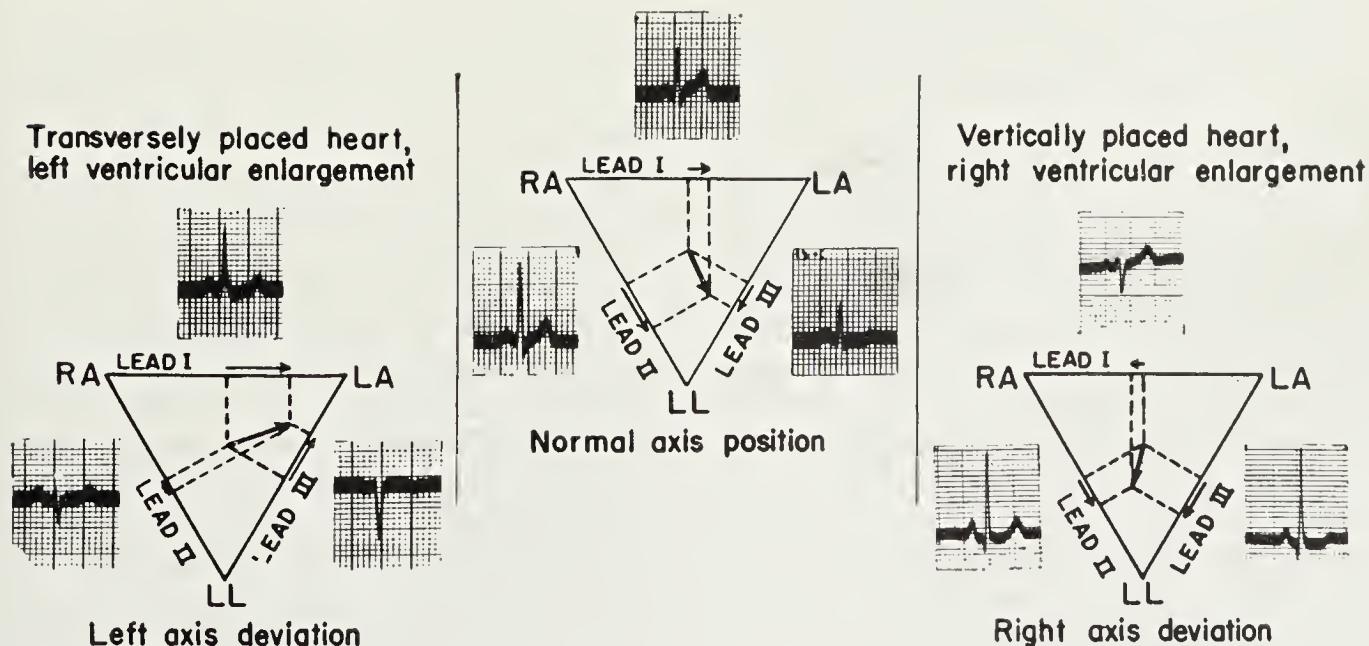


FIG. 64. Estimation of the "modal electrical axis" from standard leads. The direction of the modal axis on the frontal plane of the body varies with the position of the heart within the chest. It is clear why shifts to the left ("left axis deviation") result in large R waves in lead I and deep S waves in III; shifts to the right ("right axis deviation"), in deep S waves in lead I and tall R waves in lead III. (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

that the sum of the instantaneous points of an electrocardiographic deflection in leads I and III equals the corresponding point in lead II: lead I ( $V_L - V_R$ ) + lead III ( $V_F - V_L$ ) = lead II ( $V_F - V_R$ ); and obviously lead II — lead III = lead I, and lead II — lead I = lead III. This relationship is necessarily true whenever differences between three interrelated points are measured. Thus Einthoven's law is not confined to electrocardiography. It serves to check the accuracy of the recording technic.

2. If the triangle is assumed to be equilateral, the magnitude and direction of the "true" or "manifest" cardiac vector may be obtained by projecting the two components (instantaneous points of the electrocardiographic curve in two leads) toward the center of the triangle. By this means Einthoven, Fahr, and de Waart demonstrated that for any given set of standard bipolar limb leads the direction and (although this was not specifically stated) the size of the "true" cardiac vectors—i.e., the instantaneous and the modal electrical axes—could be approximated. The common practice of determining "right" and "left axis deviation" is illustrated in figure 64.

The varying directions and sizes of the "true" cardiac vectors may be made visible if a horizontal component (lead I) is placed on the horizontal plates and a vertical component (lead III or, better, a central terminal—left leg lead) is placed on the vertical plates of a cathode ray oscilloscope. The resulting record on the luminescent end of the cathode ray tube describes a loop for each electrocardiographic deflection. Each point of the loop represents one end of a frontal projection of an instantaneous axis or vector, the other end being defined by the zero position of the component leads. The area enclosed by the loop represents the *mean electrical axis* or mean vector for each deflection. Such records have been termed *vectorcardiograms* (figs. 65, 66).

Three examples of such frontal plane vectorcardiograms are illustrated in figure 66, and it is easily seen from the preceding steps how they are derived and how they may be correlated with the standard limb leads. An even more accurate picture of the vectorial forces waxing and waning throughout the cardiac cycle may be obtained if a vectorcardiogram obtained by recording from a sagittal plane is added. The

frontal and sagittal loops may be combined to yield a *spatial vectorcardiogram*. These promise to yield information not readily available by conventional electrocardiography.

If, instead of the height of a deflection, the *area* (height times duration) under an electro-

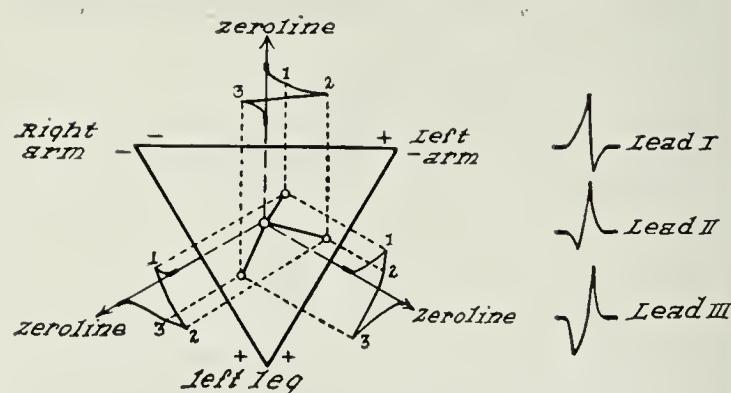


FIG. 65. Instantaneous axis of QRS and the construction of a vectorcardiogram.

Each point of an electrocardiographic curve may be plotted as outlined in figures 63 and 64. Three points of the QRS complex of a hypothetical electrocardiogram placed alongside the diagram have been chosen for geometric analysis. Their vectors vary in size and direction. The components of vector 2 are represented by the peak of R in leads I and II, and by a point in the rising limb of Q in lead III. The components of vector 3 are represented by the peak of S in I, by a point in the descending limb of R in II, and by the peak of R in III. If the peaks of all instantaneous vectors are joined by a line, a loop is formed (*vectorcardiogram*). (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

cardiographic deflection in any one lead is measured, and if the two component areas of the same deflection are projected toward the center of the triangle, the "true" or "manifest" area may be obtained as outlined above. Thus the "true" area of QRS ( $\hat{A}_{QRS}$ ) expresses the mean direction in which activation, and the "true" area of T ( $\hat{A}_T$ ) the mean direction in which recovery, passes over ventricular musculature. If recovery were simply the reverse of excitation and the length of the excitatory state were equal throughout all sections of cardiac muscle, the "true" area of QRST ( $\hat{A}_{QRST}$ ) would be zero; and in any standard limb lead the size of T would be equal to, and its direction be opposite to, that obtained for the QRS group. This is obviously not the case for the normal electrocardiogram. It must therefore be assumed that the order of recovery of the normal heart differs fundamentally from the order of excitation. It appears likely that there

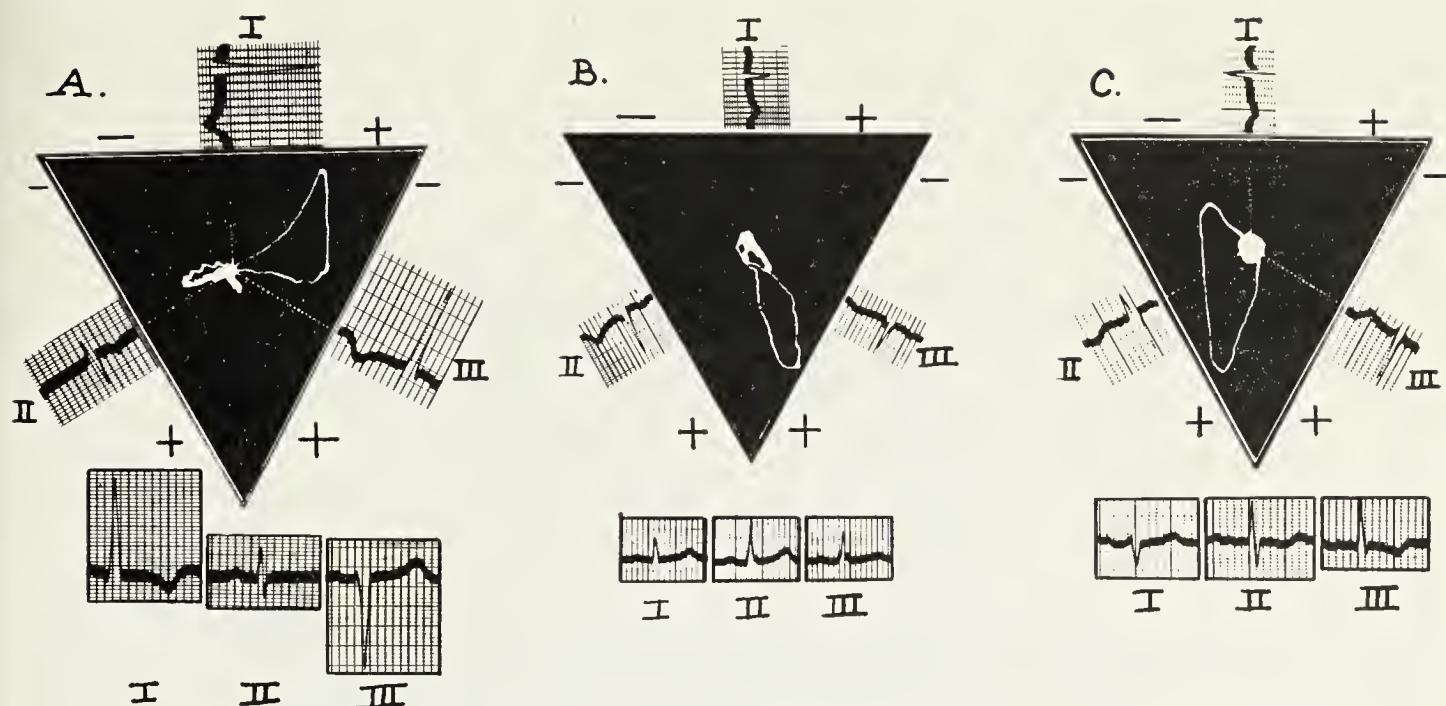


FIG. 66. Frontal plane vectorcardiograms. Records obtained from (A) a 54-year-old male subject with hypertensive heart disease, (B) a normal subject, and (C) a 31-year-old patient with mitral stenosis, auricular fibrillation, and right ventricular hypertrophy.

The vectorcardiograms are photographs of the image of an electron beam which traces the peripheral termini of the instantaneous axes on the fluorescent screen of a cathode-ray tube. The bipolar limb leads are mounted alongside the triangular frame using proper polarity. They are again reproduced below in their conventional order.

Each point on the loop represents one terminus of an instantaneous electrical axis, a line connecting the center with the point farthest away the modal axis (also illustrated in figure 64), and the area enclosed by the loop the mean electrical axis.

The small loops in A are images of the vectorcardiogram of P and T respectively. These are poorly visualized in B and C. (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

exist appreciable variations in the length of the excitatory process in various sections of normal cardiac muscle, and that these may be expressed graphically by obtaining the area of QRST ( $\hat{A}_{QRST}$ ). This total ventricular area has been termed the *ventricular gradient*. If the order of ventricular excitation is altered, as in bundle branch block or in ectopic ventricular foci, the order of recovery is likewise changed: as the area of QRS changes, the area of T is modified to an equal degree but in the opposite direction. The ventricular gradient, the area of QRST, remains unchanged. Clinical examples demonstrating abnormal T waves of this variety may be seen in figures 48 and 57. If, however, T changes independently of QRS, the total area of QRST, the ventricular gradient, will change. The ventricular gradient, therefore, becomes a means by which T wave changes may be expressed in a semi-quantitative fashion. It may be seen that the concept of the ventricular gradient points clearly to two major causes of T wave changes: (1) those associated with changes in QRS with the ven-

tricular gradient remaining unaltered (secondary T wave changes), and (2) changes independent of QRS with shifting of the ventricular gradient (primary T wave changes).

The size and direction of  $\hat{A}_{QRST}$ , the ventricular gradient, varies considerably even when no striking change in the order of recovery is noted. The exact location of the heart in the thoracic cage differs widely from subject to subject, and it may be assumed that the ventricular gradient and its projection on the frontal plane of the body are influenced by the spatial position of the heart. In turn, the position of the heart within the chest may be inferred from an analysis of the ventricular gradient. Estimations of the ventricular gradient, performed by measuring time lines and millimeter division of the conventional records, and expressed in terms of millivolt seconds, may therefore serve two useful purposes: (1) to provide a geometric expression of primary changes of T and RST segment, and (2) to obtain information on the position of the heart within the chest.

It is to be stressed that the vectorial analysis of the electrocardiogram which includes (a) the estimation of the electrical axis and the "vectorcardiogram," (b) conclusions drawn from calculated ventricular gradients, and (c) the interpretation of the nature of unipolar limb leads (obtainable only by the use of the central terminal, which in turn is based on the concept of the equilateral triangle) are, at best, first approximations. The heart is not located at the center of an equilateral triangle, and the effects of large sections of cardiac muscle ("silent regions") perpendicular to the plane of the standard limb leads are not included in calculations made from them. The concepts, however, are fundamental, and the objections that may be raised have not altered the useful information that their application has provided.

**Further Uses of Ventricular Gradient and of Unipolar Limb Leads: Spatial Position of Heart.** The vectorial concept of the electrical axis was introduced by Einthoven, who thought that significant shifts of the modal electrical axis of QRS could be correlated with ventricular hypertrophy. Subsequent observations have failed to demonstrate a close correlation between ventricular preponderance and axis deviation. Shifts of the average vector of QRS to the left occur in horizontally placed hearts; shifts to the right, in vertically placed hearts with or without ventricular enlargement (fig. 64). The previous discussion has already revealed that the "manifest" or "true" vectors and areas calculated from the standard limb leads are again only projections of spatial vectors upon the frontal plane of the body, and that in the conventional diagrams of figures 63, 64, and 65 spatial relationships are disregarded. In recent years, however, the analysis of unipolar limb leads and calculations of the relationship of the ventricular gradient to the long axis of the heart have revealed independently that the *spatial position of the heart* within the chest profoundly influences the electrocardiographic pattern of various leads.

In the normal heart (fig. 62) the right ventricular pattern is generally deflected to the left arm. It suggests that the right ventricle occupies an anterior position and that it forms the upper left lateral margin of the heart in the anteroposterior position. The left ventricular pattern is deflected to the left leg, making the location of the left

ventricle posterior and inferior. The heart is in a vertical position. In obese persons, or when for other reasons the heart assumes a horizontal position, the left ventricular pattern shifts to the left arm, the right ventricular pattern to the left leg, and  $V_1$  and  $V_F$  completely reverse their configuration (fig. 67 A). By summatting ( $V_L$ ) and ( $-V_R$ ) to obtain lead I, and ( $V_F$ ) and ( $-V_L$ ) to obtain lead III, a vertical position (with the right ventricular pattern deflected to  $V_L$ ) will result in "right axis deviation" (figs. 64, 67 B), a horizontal position (with the left ventricular pattern deflected to  $V_L$ ) in "left axis deviation" (figs. 64, 67 A). The S waves of lead I in the former and of lead III in the latter case are the representations of the right ventricular pattern as recorded from the respective extremities and incorporated into the bipolar electrocardiogram. These changes can be interpreted only as representing rotation of the heart around its longitudinal axis. Rotation on this axis must be predominantly responsible for "axis deviations" of the standard limb leads of the kind charted in figs. 64 and 67 A and B.

By supposing that the duration of the excitatory state of various cardiac regions is similar in the majority of normal human hearts, Ashman has postulated that the spatial position of the ventricular gradient should be nearly identical from heart to heart and that the projection (1) of the true (spatial) area of QRS and (2) of the spatial gradient (area of QRST) upon the frontal plane of the body should bear a constant relationship to the long axis of the heart. If the heart be rotated around any of its three anatomic axes, the projection of  $\hat{A}_{QRST}$  will change according to degree and direction of rotation. By using three axes of an experimental model representing the long axis of the heart, the area of QRS, and the spatial gradient, Ashman deduced how rotation around all three anatomic axes of the heart would affect the projection of the ventricular gradient and of the area of QRS on the frontal plane of the body and how, in turn, these rotations should influence the configuration of the ventricular deflection of a standard lead electrocardiogram. Similar information is now being obtained by the use of spatial vectorcardiograms.

In a nonrotated heart the long axis of the heart, the vector representing the ventricular gradient, and the vector representing the area of QRS very nearly overlap when projected on the

frontal plane. The long axis points downward and forward, the gradient downward and backward, and the area of QRS straight backward, the latter two vectors forming angles of  $60^\circ$  and  $90^\circ$  with the long cardiac axis. Any degree of

cardiogram which has evolved from these still theoretic considerations. It evolves that the spatial position of the heart appears to have a profound influence on the electrocardiogram in standard bipolar leads, in frontal plane and

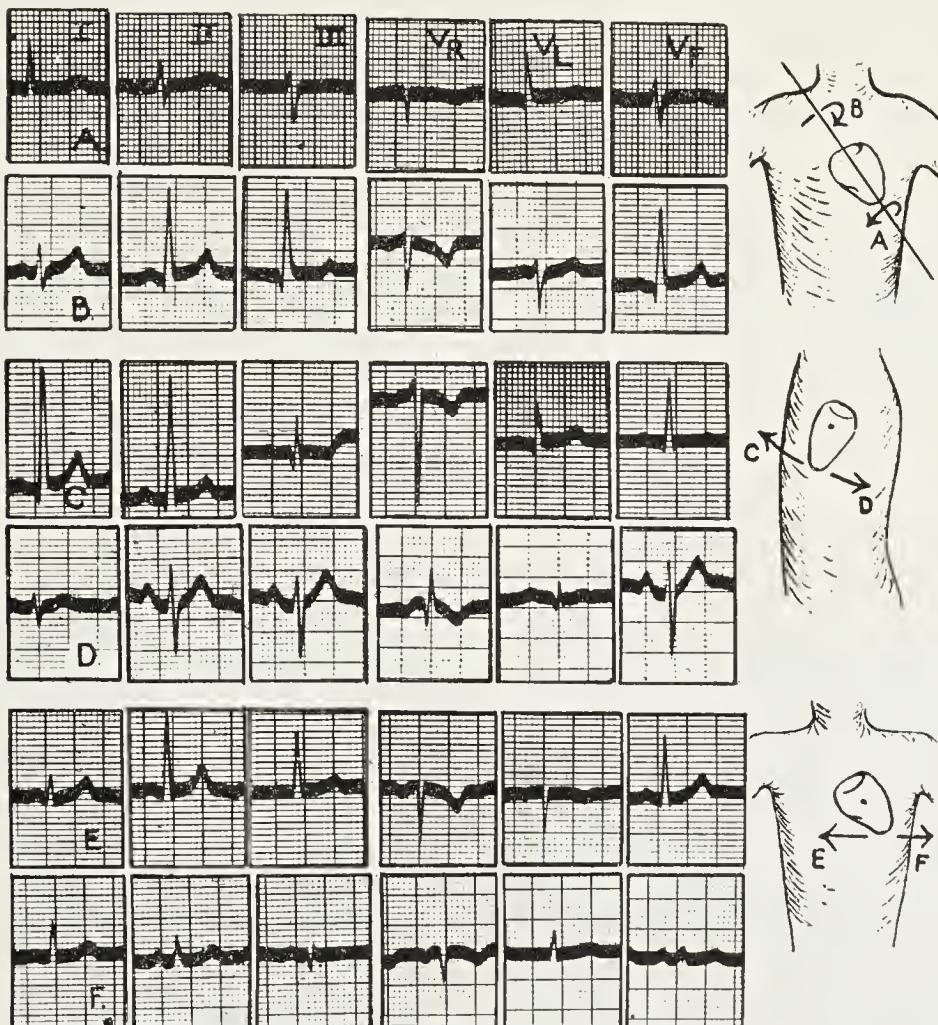


FIG. 67. The spatial position of the heart within the chest. Rotation of the heart around its three axes.

(A, B) Rotation around the long axis of the heart causes "left and right axis deviation." Unipolar limb leads  $V_L$  and  $V_F$  display right and left ventricular pattern respectively. (A) Left axis deviation. (B) Right axis deviation. (C, D) Rotation around the transverse axis influences the size of Q and S waves in standard leads, and alters the configuration of QRS in  $V_R$ . (C) Apex forward. (D) Apex backward. (E, F) Rotation around anteroposterior axis contributes to "axis deviation." Note the similarity of  $V_R$  and  $V_L$  in the vertical heart of E. (E) Shift to right. (F) Shift to left. (Courtesy, Hecht: "Basic Principles of Clinical Electrocardiography," American Lecture Series, Springfield, Charles C Thomas, Publisher.)

rotation changes this relationship in a predictable manner.

Examples of standard limb leads representing six variations of the rotation of the heart on its three axes are illustrated in figure 67. The corresponding unipolar limb leads have been added. The illustration and its legend will help to explain some of the normal variations of the detailed configuration of the extremity electro-

spatial vectorcardiography, in unipolar limb leads, and in semidirect esophageal leads. It is of little concern in the interpretation of the standard semidirect precordial leads.

#### FORM OF ABNORMAL ELECTROCARDIOGRAM

The interpretation of an abnormal electrocardiogram rests ultimately on a rational experi-

mental basis along lines discussed in previous sections. It should be stressed that if the form of an electrocardiogram appears unusual, either the positions of the heart with respect to the recording electrodes or the ordinary sequence of depolarization and recovery are changed, and that these modifications are not a priori evidence of a mechanically failing heart. The integration of an abnormal electrocardiographic finding into the clinical evaluation of the patient should be attended to with great reservations. As a general rule it is better to have overlooked an obvious abnormality than to have overemphasized insignificant changes. Certainly, the common electrocardiographic diagnosis of "myocardial damage" based on minor and unspecific electrocardiographic changes is meaningless and harmful. In interpreting an electrocardiographic tracing one should emphasize the nature of the electrophysiologic abnormality present, and this should be stated in detail. A clinical diagnosis has no place in an electrocardiographic report, because the clinical significance of the record may not be apparent and in many instances will require repeated and detailed electrocardiographic explorations. Judgment is often deferred, and the value of serial examinations over days or weeks cannot be overemphasized. Careless overconfidence has caused untold harm and has led to "the present wretched state of electrocardiographic diagnosis" and "to the misery attributable to it" (Wilson *et al.*, 1947). (See Chapter 235.)

In the pages to follow, abnormalities of the individual deflections will be listed, followed by a discussion of the more complex combined patterns of QRS and T common to certain pathologic states. As in the previous sections, the discussion commences from the shape of direct or semidirect leads, because when these are understood the interpretation of the records from regions to which the potential variations observed in semidirect leads are deflected becomes largely self-evident.

**Abnormal P Waves: AURICULAR ENLARGEMENT.** (See figure 68.) Enlargement of the left auricle causes a delay in conduction of impulses through posterior auricular mass. This results in a delayed intrinscoid auricular deflection in high esophageal leads, and in a sharply biphasic P in V<sub>1</sub> of the plus-minus type (fig. 68 A) P increases in width (0.12 second and over), and in standard leads, usually in lead I, P<sub>QRS</sub> assumes

a broad and notched appearance (*mitral P wave*). Right auricular enlargement cannot be detected by present electrocardiographic technics, but in conditions causing predominant distention of right auricular mass (increased pulmonic pressure) the electrical effects of the right auricle are particularly well projected toward the diaphragmatic surface. In consequence, tall and peaked, but usually not broadened, P waves appear in lower esophageal leads, in V<sub>F</sub>, and therefore in leads II and III (*pulmonic P wave*) (fig. 68 B). P in V<sub>1</sub> may be biphasic but the changes are usually less striking than in the mitral type. The pulmonic P wave may regress under treatment; the mitral P does not.

**DISTURBANCE OF INTRA-AURICULAR CONDUCTION.** (See figure 68 C). Unusual slurring and notching with broadening of P appear at times in subjects without evidence of auricular enlargement, particularly during prolonged bouts of rheumatic fever, in arteriosclerotic heart disease, or following large doses of quinidine. These changes are regarded as instances of intra-auricular block. They often precede, as does the mitral P wave, the onset of auricular fibrillation.

**CHANGES OF P<sub>T</sub>.** Deformations of the PR interval, if striking, are caused by unusual auricular recovery. Occasional instances of auricular infarction may thus be detected, but, in general, alterations of P<sub>T</sub> are of no particular concern.

**Abnormal QRS Group: VOLTAGE.** QRS deflections, particularly in semidirect leads, tend to be large in young individuals and in slender persons. They are reduced in voltage in large individuals and in obese subjects. Unusually small QRS groups (*low voltage*) are recognized if the largest QRS deflection does not exceed one half of the accompanying standardization deflection in standard limb leads. Low voltage is occasionally, but not necessarily, seen in diffuse pericarditis, in severe anasarca and in untreated myxedema. More often than not no ready explanation of the phenomenon can be offered, and its clinical significance remains in doubt. It has been observed in healthy subjects. Low voltage is commonly observed only in standard bipolar limb leads. If seen in precordial leads, it is usually an accompaniment of changes pointing to tissue destruction (myocardial infarcts) and may be obtained over a scarred area or over a region of a ventricular aneurysm. Very large QRS deflections (*high voltage*), in precordial leads exceeding

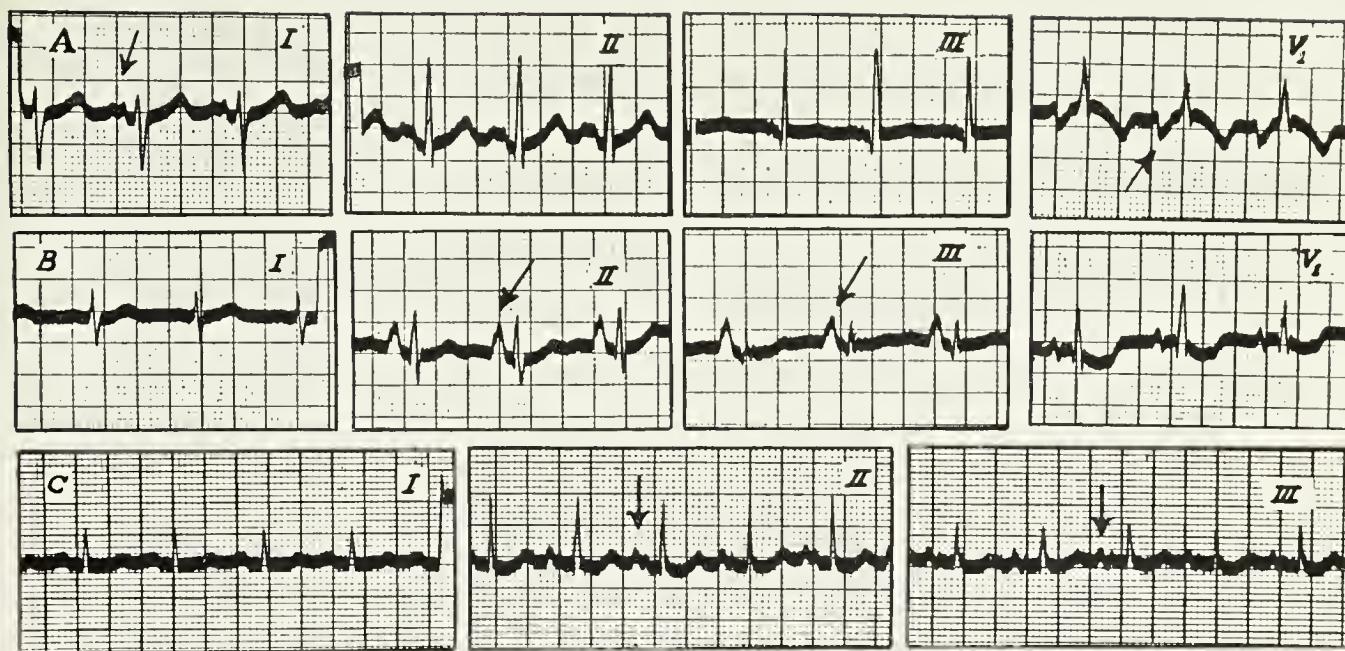


FIG. 68. Abnormal P waves. (A) "Mitral" P wave (left auricular enlargement) in a 14-year-old boy with pure mitral stenosis. (B) "Pulmonic" P wave (right auricular distension) in a 57-year-old coal miner with pulmonary fibrosis and acute exacerbation of a chronic cor pulmonale. (C) Disturbance of intra-auricular conduction in a 67-year-old carpenter with paroxysms of auricular fibrillation. This record was obtained a day after successful termination of an attack by quinidine sulfate. Time lines: 0.2 second, 10 mm. = 1 mv. Film speed: 25 mm./sec.



FIG. 69. Bundle branch block.

(A, top and bottom) Left bundle branch block: broad and notched QRS complexes in standard bipolar limb leads without S in I and in V<sub>L</sub>; tall deflections with deep S waves and small R over right ventricle, late intrinsicoid deflection over left ventricle. The subject is a 55-year-old laborer with arteriosclerotic heart disease.

(B, top and bottom) Right bundle branch block: broad and notched QRS complexes in standard bipolar limb leads with conspicuous S waves in I and late broad R waves in V<sub>R</sub>. Late intrinsicoid deflection over right ventricular surface (transition from right to left ventricular pattern here between V<sub>3</sub> and V<sub>4</sub>). The subject is a 62-year-old mechanic with arteriosclerotic heart disease.

Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 50 mm./sec.

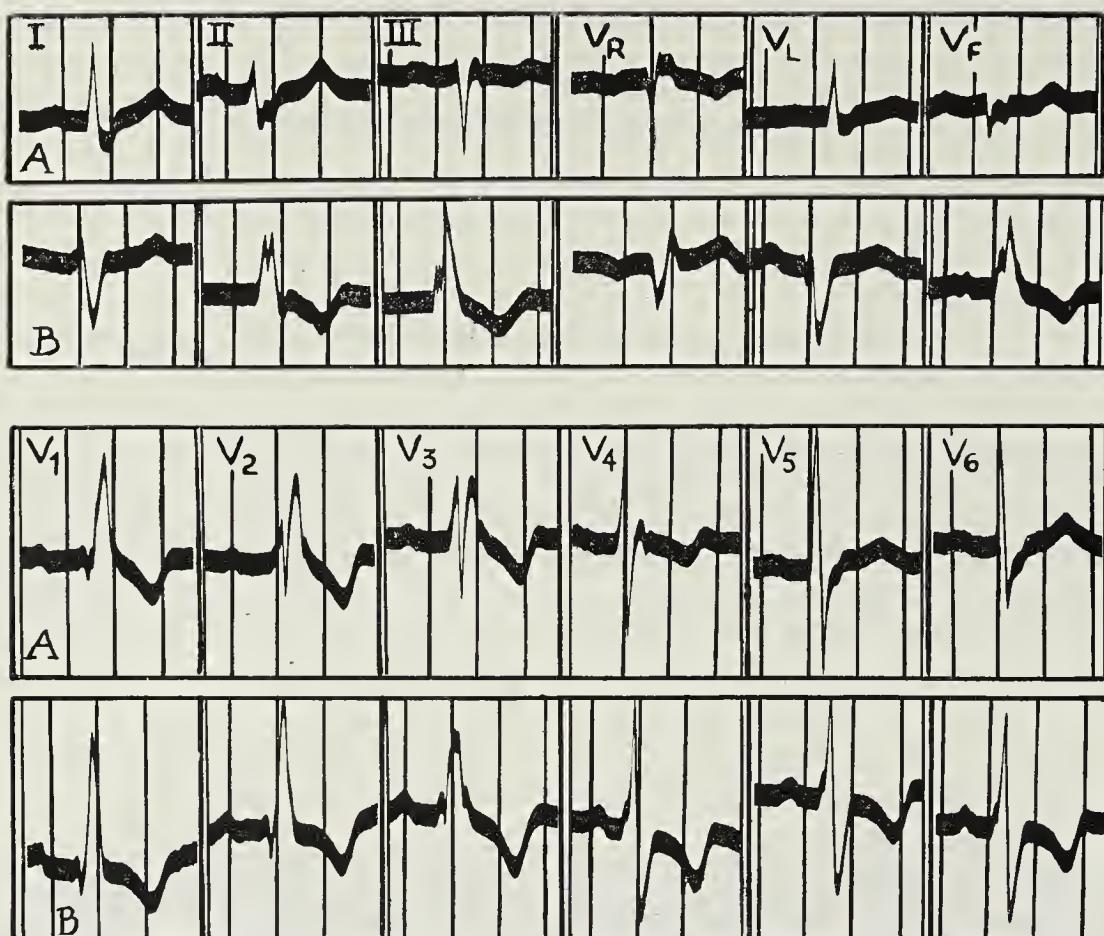


FIG. 70. Influence of position of the heart upon the configuration of QRS in bundle branch block. Two examples of right bundle branch block with broad S in I, late R in  $V_R$ , and delayed activation of epicardial surface of right ventricle ( $V_1$ ,  $V_2$ ,  $V_3$ ).

(A) Standard and unipolar limb leads suggest a horizontally placed heart ("left axis deviation") in a subject with hypertensive heart disease.

(B) Standard and unipolar limb leads suggest a vertically placed heart ("right axis deviation") in a patient suffering from acute right ventricular dilatation and rheumatic heart disease with mitral stenosis.

Note that regardless of the different "axis deviation" in limb leads the QRS complexes in the precordial leads of the two subjects are almost identical.

Changes of this magnitude are less likely to occur in left bundle branch block where "left axis deviation" is a very common, though not an invariable, finding.

Time lines: 0.2 second, 10 mm. = 1 mv. Film speed: 25 mm./sec.

3 mv., in standard 2.3 mv., are usually indicative of ventricular enlargement (see p. 356) unless they represent an exaggerated normal response in individuals with thin chest walls or in subjects who have undergone a rib resection with collapse of the normal thoracic contour where the exploring electrode comes almost in contact with cardiac muscle. Large QRS deflections of the QS or S type are seen regularly in ventricular enlargement and in bundle branch block over the contralateral ventricle (fig. 69).

**DELAY IN INTRAVENTRICULAR CONDUCTION.** (See figures 57, 69, 70, 71.) Slurring and notching of QRS complexes in standard bipolar limb leads are considered evidence of disturbed intraventricular conduction, only when these changes may also be seen in unipolar limb leads and in

semidirect leads. If, in addition, the QRS complexes increase in width, the underlying lesion may be assumed to involve the ventricular conduction system proper. If QRS measures more than 0.12 second, *bundle branch block* is present unless severe electrolyte disturbances or the influence of quinidine and quinidine-like compounds have resulted in extensive and uniform depression of cardiac conductivity (see p. 389).

The site of the lesion is best determined by estimating the onset of the intrinscoid deflection in precordial leads (figs. 57, 58, 69, 70, 71). The onset of this deflection is delayed in  $V_1$ ,  $V_2$ , and  $V_3$  in right bundle branch block (more than 0.07 second from the beginning of QRS), and equally delayed in  $V_5$  and  $V_6$  in left bundle branch block (table 38). In the latter,  $V_L$  usually resembles  $V_5$

or  $V_6$ , and  $V_R$  may either show a broad but uniformly downward directed QRS group or, if rotation is such as to allow the effects of the left ventricular cavity to be deflected to the right arm as well,  $V_R$  may also become upright. In

occur as the result of a belated activation of the right ventricle from the contralateral side.

In standard limb leads, right bundle branch block is generally characterized by a deep and slurred S wave in lead I, left bundle branch block

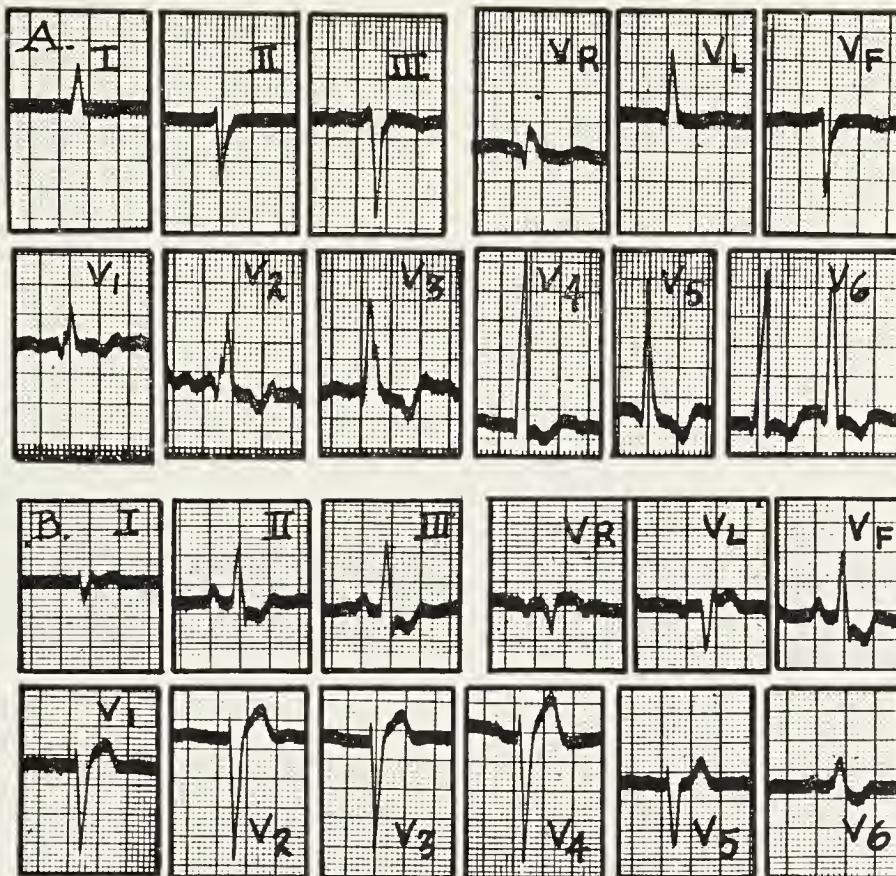


FIG. 71. Failure of standard limb leads alone to localize conduction defects.

(A) Record of a 66-year-old male with arteriosclerotic heart disease and unexplained granulocytopenia. QRS measures 0.15 second and "left axis deviation" is present. The configuration of lead I suggested left bundle branch block.  $V_R$ ,  $V_1$ ,  $V_2$ , and  $V_3$  clearly reveal belated activation of the right ventricle (right bundle branch block); left ventricular leads are compatible with left ventricular enlargement. The record presents an example of a horizontally placed heart with left ventricular hypertrophy and right bundle branch block. Auricular fibrillation is present.

(B) Electrocardiograms of a 74-year-old laborer with chronic obstructive emphysema. QRS measures 0.12 second. "Right axis deviation" is noted with a deep, though somewhat unusual,  $S_I$ . Serial precordial leads clearly indicate localized delay of intraventricular conduction of the left ventricle (left bundle branch block). The record presents an example of a vertically placed heart with left bundle branch block. (The changes of ST segment and T waves are caused by digitalis therapy.)

(Note: "Atypical" conduction defects can usually be lateralized by semidirect leads.)

Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

right bundle branch block the major section of QRS is always upright in  $V_R$ . It indicates delayed and altered activation of the right ventricular endocardial surface (figs. 58, 59, 70). The changes in shape of  $V_R$  in right bundle branch block are as diagnostic as the delay of the intrinsicoid deflection over the right ventricle because both

by a single, wide, and splintered upright deflection (R), without either Q or S waves (fig. 69).

The presence of  $S_I$  in right bundle branch block again expresses delayed activation of the right ventricular cavity and is caused by the late upright R in  $V_R$  which enters lead I as a

Table 38

ONSET OF THE INTRINSICOID DEFLECTION (PEAK OF LATEST R WAVE) IN THE NORMAL AND ABNORMAL ELECTROCARDIOGRAM (IN MILLISECONDS)

	<i>V</i> <sub>1</sub>	<i>V</i> <sub>2</sub>	<i>V</i> <sub>3</sub>	<i>V</i> <sub>4</sub>	<i>V</i> <sub>5</sub>	<i>V</i> <sub>6</sub>
Normal.....	17 (6-33)	19 (3-39)	31 (13-49)	34 (23-55)	34 (25-53)	39 (37-50)
Left ventricular hypertrophy..	13 (0-30)	10 (0-30)	30 (0-70)	41 (0-70)	48 (30-70)	49 (30-80)
Left bundle branch block.....	8 (0-15)	13 (0-25)	15 (5-30)	25 (10-65)	58 (20-95)	88 (35-175)
Right ventricular hypertrophy	39 (25-49)	32 (10-43)	..	..	23 (15-28)	21 (10-39)
Right bundle branch block....	95 (60-135)	88 (40-140)	67 (35-120)	52 (25-105)	41 (25-85)	40 (25-65)

These figures are approximate and based on the authors' own material and that published by:

C. E. Kossmann and F. D. Johnston: *Am. Heart J.*, **10**:925, 1935.

G. B. Myers, H. A. Klein, and B. E. Stofer: *Am. Heart J.*, **35**:1, 1948.

D. Sodi Pallares, O. Paras, E. C. Cosio, and F. Mendoza: *Arch. Inst. cardiol. México*, **16**:397, 1946.

M. Sokolow and T. P. Lyon: *Am. Heart J.*, **37**:161, 1949.

negative value ( $I = V_L - V_R$ ). The absence of Q in lead I in left bundle branch block represents failure of the left side of the septum to be activated (fig. 58, p. 356). Positional changes of the heart within the chest are primarily responsible for the degree of "axis deviation" that may exist, and these may tend to alter the shape and direction, though not the width, of the QRS complexes in standard leads. As in the normal, positional changes of the heart have little bearing on the form of the electrocardiogram in precordial leads. Examples of right bundle branch block in a vertically and in a horizontally placed heart are illustrated in figure 70.

The T wave following the abnormal QRS group points in the opposite direction and the area of T equals the negative area of QRS so that in uncomplicated bundle branch block the ventricular gradient (area of QRST) retains the value that it had when normal conduction was present ("secondary" T wave changes, fig. 69, p. 357). An example of left bundle branch block with wide QRS in lead I and upright "normal" T waves would indicate a change in ventricular gradient over and in addition to the conduction defect. Such records should be viewed with more concern than examples of bundle branch block which display the usual inversion of T in lead I.

*Incomplete bundle branch block* is recognized if all of the above criteria are present but QRS does not exceed 0.12 second in width (fig. 57); *transient bundle branch block* and *unstable bundle branch block* (p. 350) are recognized if the abnormal complexes vary from beat to beat or from

examination to examination, or if the abnormal complexes occur only at faster rates.

Pre-excitation phenomena with wide QRS complexes and short PR intervals (*Wolff-Parkinson-White syndrome*), although superficially resembling bundle branch block, need be differentiated from the latter as evidence is now available which suggests that the bundle and its branches function normally in most instances of this disorder (p. 356). Bundle branch block associated with myocardial infarction will be discussed below.

**Primary T Wave Changes (Abnormal T Waves and Abnormal RST Segments with Displacement of RT Junction).** The order of repolarization in an otherwise normal heart is easily upset. T wave changes of the primary type, expressed as changes in the ventricular gradient, occur if the length of the excitatory state of various sections of cardiac muscle is altered (p. 357). Such changes are readily induced by anxiety and fear, by injection of epinephrine, by autonomic imbalance not necessarily associated with emotional factors, by food intake (particularly of cold and carbonated drinks), by postural changes, and by alterations in the intracellular electrolyte balance. They are often "corrected" by sympatholytic or adrenergic compounds. "Abnormal" T waves can thus be readily induced experimentally in normal subjects and the correct interpretation of changes in the ventricular gradient may become exceedingly difficult.

Two examples of abnormal gradients in physically healthy subjects are illustrated in fig. 72.

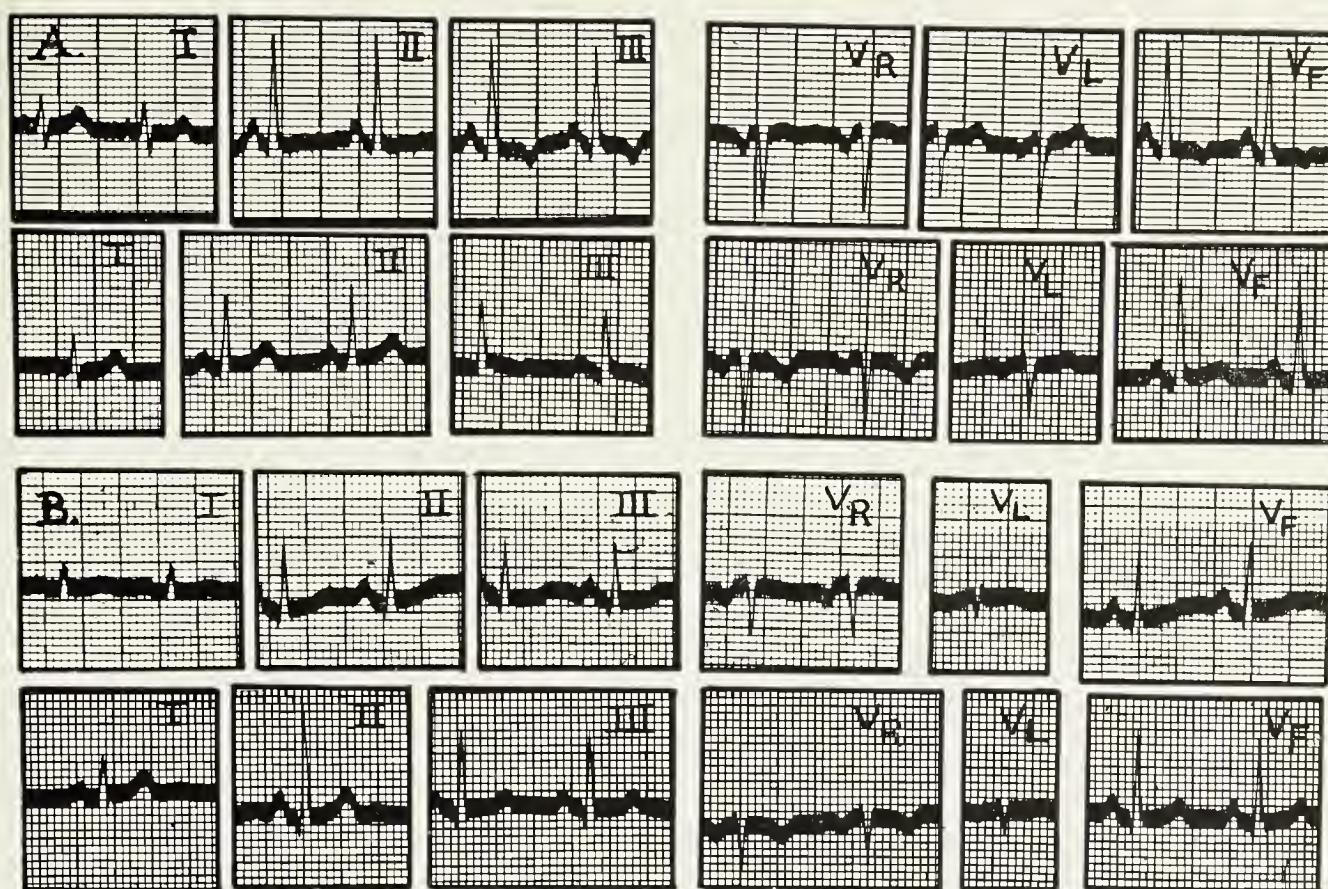


FIG. 72. Abnormal T waves and abnormal ventricular gradients in normal subjects.

(A) A 32-year-old normal male (perirectal abscess), first examined on 3-31-49. The electrocardiogram reveals flat T with inversion of terminal portion in lead II and inversion of T in  $V_f$ .  $V_R$  shows a biphasic final deflection. The record is "abnormal." On 4-8-49, T has become upright in II and  $V_f$  and inverted in  $V_R$ . The record is now "normal." No obvious cardiac involvement was present at any time.

(B) A similar change involving the RST segment of lead II, lead III,  $V_f$ , and  $V_R$  is noted in this 28-year-old schizophrenic male. No evidence of heart disease was present and no medication was taken.

(Note: Similar records may be obtained during and following the injection of epinephrine, and many changes of this type are readily reversible by vagal stimulation, or by sympatholytic and adrenolytic compounds.)

Time lines: 0.04 and 0.20 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

It would have been impossible to exclude myocardial involvement had these subjects suffered, let us say, from infections or from certain metabolic disorders at the time of the examination. Contrariwise, normal electrocardiographic tracings with normal or only slightly altered ventricular gradients may be obtained in severe congestive heart failure or even in patients dying from heart disease. Although these are not common occurrences, it should be obvious that it is rash to judge mechanical efficiency of cardiac musculature from the electrocardiogram and in particular from T wave changes alone.

It was pointed out (1) that local delay of repolarization in a given section of cardiac muscle alters the shape of the final portion of T, and (2) that failure to repolarize completely in diastole results in shifts of the RST segment and displacement of the RST junction above or below

the isoelectric line. These two types of changes represent quantitative differences related to the degree of the underlying electrophysiologic disturbance, one merging into the other. If one adds to this that the direction of T wave changes and RST segment shifts is dependent on the location of the involved region with respect to the exploring electrode, a concept emerges that has at least the advantage of simplicity (fig. 73). It is reasonably well established that lesions involving the epicardial surface result in terminal inversion of T and, if more severe, in elevation of the RT junction in direct or semidirect leads obtained from the vicinity of the regions involved. Inversely, it is likely that endocardial repolarization delay exhibits upright T waves and, if more severe, depression of the RT junction in direct or semidirect leads. Unipolar limb leads ( $V_R$ ) dominated largely by endocardial effects will show the opposite changes.

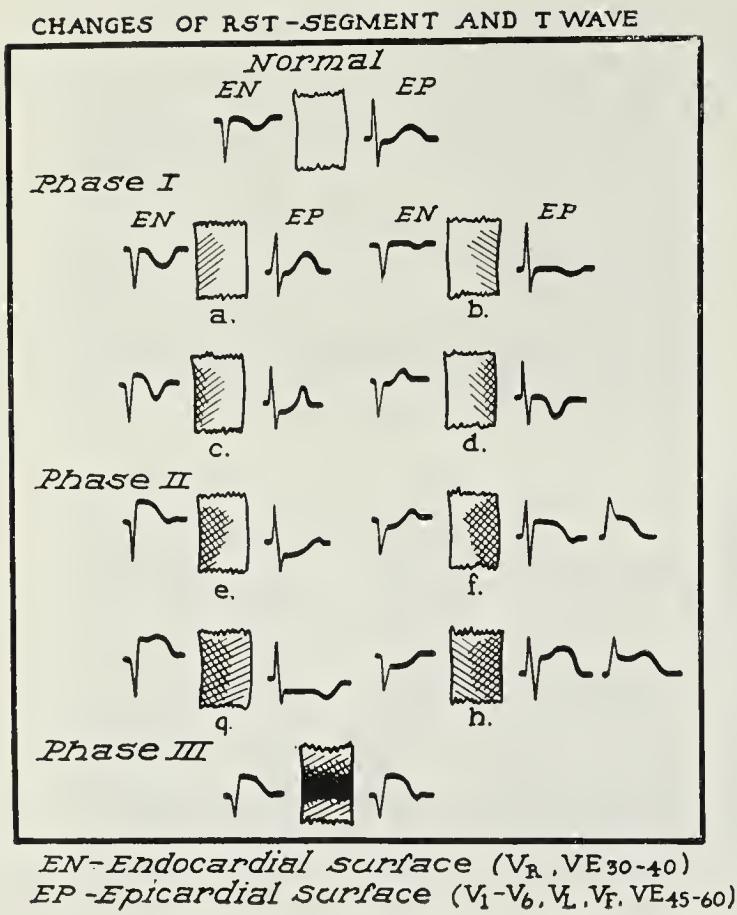


FIG. 73. A working concept of changes in semidirect leads confined to the process of repolarization (RST segment and T wave).

A section of heart muscle is shown with the endocardial surface (EN) facing to the left, the epicardial surface (EP) to the right. Delay in repolarization predominantly involving subendocardial regions is illustrated in the left-hand column, that confined to subepicardial regions in the right-hand column. The intensity of the process is indicated by hatching and crosshatching.

Delay in subendocardial repolarization causes increase in the height of T in precordial leads (a, e), and failure of complete subendocardial repolarization causes depression of the RT junction (e, g). Delay in subepicardial repolarization results in inversion of the terminal portion of T in precordial leads (b, d), while failure of complete repolarization results in diastolic elevation of RT junction (f, h).

When applied to the pattern of coronary insufficiency, phase I represents the stage of ischemia (Bayley), phase II represents that of injury (Bayley), and phase III indicates transmural myocardial necrosis with surrounding zones of injury and ischemia (see also figure 80). (Courtesy, Hecht: *Arch. Int. Med.*, **84**:711, 1949.)

As an example, a precordial lead may show four types of T wave changes:

1. Slight delay of endocardial repolarization: upright T waves, no significant deviation of RT junction and ST segment (the normal adult precordial electrocardiogram) (fig. 62).

2. Failure of complete diastolic repolarization confined primarily to subendocardial muscle layers: depression of the RT junction and ST segment, the terminal portion of T often remaining positive (type: toxic myocardial changes, anoxemia, digitalis) (fig. 75).

3. Delay of epicardial repolarization: inversion of terminal portion of T without appreciable shifts of the RST segment (type: trauma, mild pericarditis, subacute and old myocardial infarction) (figs. 74, 75).

4. Failure of diastolic repolarization confined primarily to subepicardial muscle layers: elevation of the RT junction and ST segment with or without terminal inversion of T (type: pericarditis, acute myocardial infarction) (fig. 79).

Combinations of these four types occur frequently and account for the great variety of abnormal shapes of the final ventricular deflection. It should be added that relatively minor changes of subepicardial muscle layers will outweigh larger involvement of subendocardial layers, and that a small epicardial region that fails to repolarize may cause profound elevation of the RT junction in a precordial electrocardiogram while only relatively large involvements of distant (subendocardial) regions are capable of influencing the precordial electrocardiogram. Semidirect leads influenced primarily by endocardial regions (high esophageal leads,  $V_R$ ) obviously demonstrate alterations opposite to those listed above.

A normal upright T should therefore denote a certain degree of endocardial repolarization delay. This is characteristic for the adult electrocardiogram where apparently the length of the excitatory state of subendocardial layers exceeds that of subepicardial regions. Abnormal electrocardiograms of the kind indicating subepicardial lesions (see figure 74) with T wave inversion would indicate that these normal differences have been wiped out. If further injurious effects are brought to bear on such hearts, either the RST segment becomes elevated because the degree of injury of the abnormally responding region is further increased, or the previously inverted T waves become upright (*paradoxic reversal* of T). They assume a more "normal" appearance because involvement of distant layers, over and in addition to the subepicardial region already present before the new injury, reestablishes the nor-

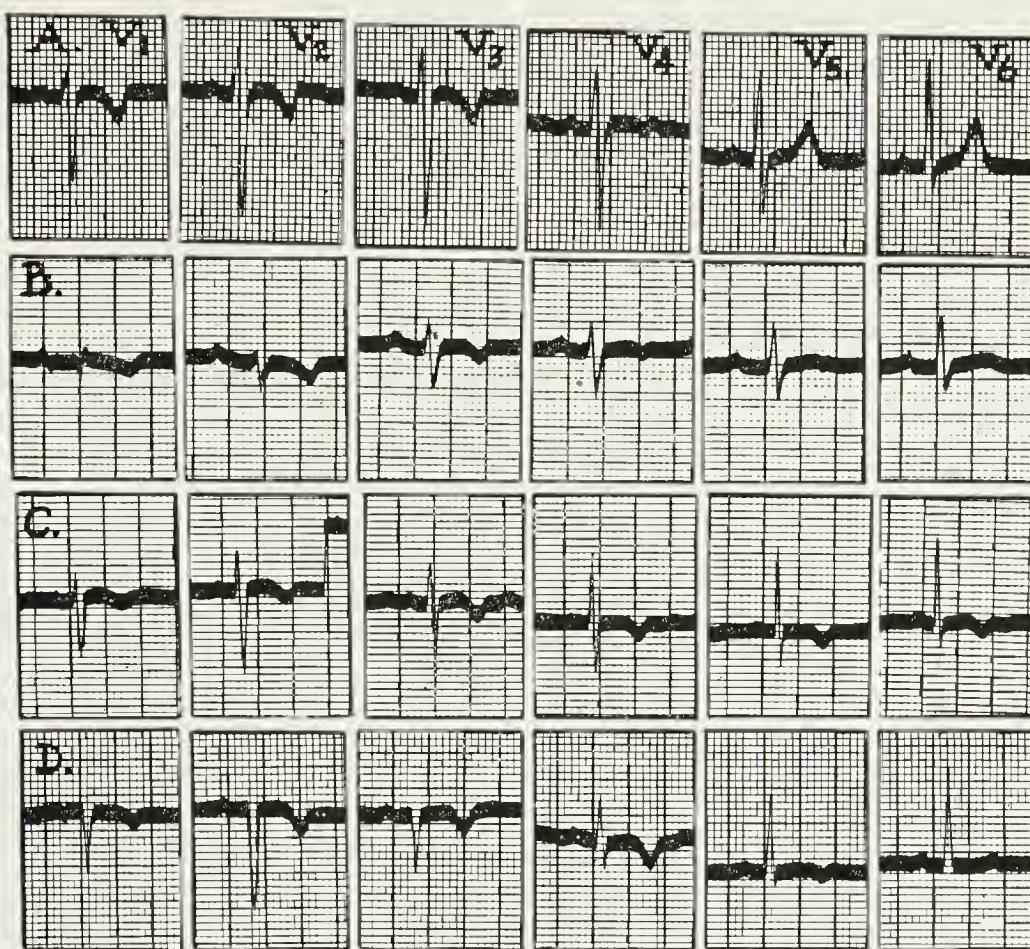


FIG. 74. T wave changes suggesting "delay of subepicardial repolarization." All examples demonstrate inversion of the terminal portion of T in precordial leads. (A) A normal electrocardiogram of a 10-year-old child with inversion of T in V<sub>1</sub>-V<sub>3</sub> and biphasic T in V<sub>4</sub>. (B) T wave changes in five of six chest leads accompanying pericarditis in a 27-year-old woman with lupus erythematosus disseminatus. (C) Acute bromide intoxication in a 63-year-old housewife. (All chest leads returned to normal upon recovery. The exact clinical significance of the electrocardiographic changes remains obscure.) (D) T wave changes following an episode of myocardial infarction in a 61-year-old woman (note QRS changes in V<sub>2</sub> and V<sub>3</sub> as well). Time lines: 0.04 and 0.20 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

mal relationships but on a pathologic level (see figure 81).

Direction and shape of RST segment and T waves in standard bipolar limb leads are, of course, directly related to changes in semidirect leads. Their interpretation is complicated by their bipolarity. A given alteration of the final deflection in standard limb leads may result from changes of either of one of the two component unipolar limb leads or from a combination of T wave changes deflected to both extremities. The nature and origin of T wave changes cannot be evaluated by the use of bipolar limb leads alone.

The alterations of the final deflection that may be induced depend largely on the previous state of the heart muscle. They are modified by pre-existing abnormalities. There is, therefore, no characteristic electrocardiogram denoting certain clinical conditions or drug effects. It is common, however, to find certain T wave abnormalities

frequently associated with certain clinical findings (see legends to figures 74, 77).

**Abnormal QT Interval.** The excitatory state of the entire ventricular musculature may be prolonged, and with or without T wave changes the length of "electrical systole" measured from the beginning of Q to the end of T may be altered. These changes are generally independent of the mechanical systole as measured by the distance from the first to the second apical heart sound.

**PROLONGATION OF QT INTERVAL.** This is almost regularly present in severe myocardial depression as seen in acute myocarditis following quinidine medication or during an episode of myocardial infarction. Without evidence of heart disease it is frequently present in sympathetic stimulation of heart muscle and may be considered a characteristic feature of the electrocardiogram in certain electrolyte disturbances, particularly in hypocalcemia (serum Ca level

below 7 mg. %) and, associated with other abnormalities, in hyperkalemia and hypokalemia. Simple prolongation of QT with an otherwise normal pattern is diagnostic of hypocalcemia in chronic nephritis or in tetanic states.

the attack. When circulatory impairment causes gross tissue destruction and *infarction of the myocardium*, a triad of changes takes place that involves both the QRS complex and the T wave:

#### REDUCTION OF TOTAL VOLTAGE OF QRS WITH

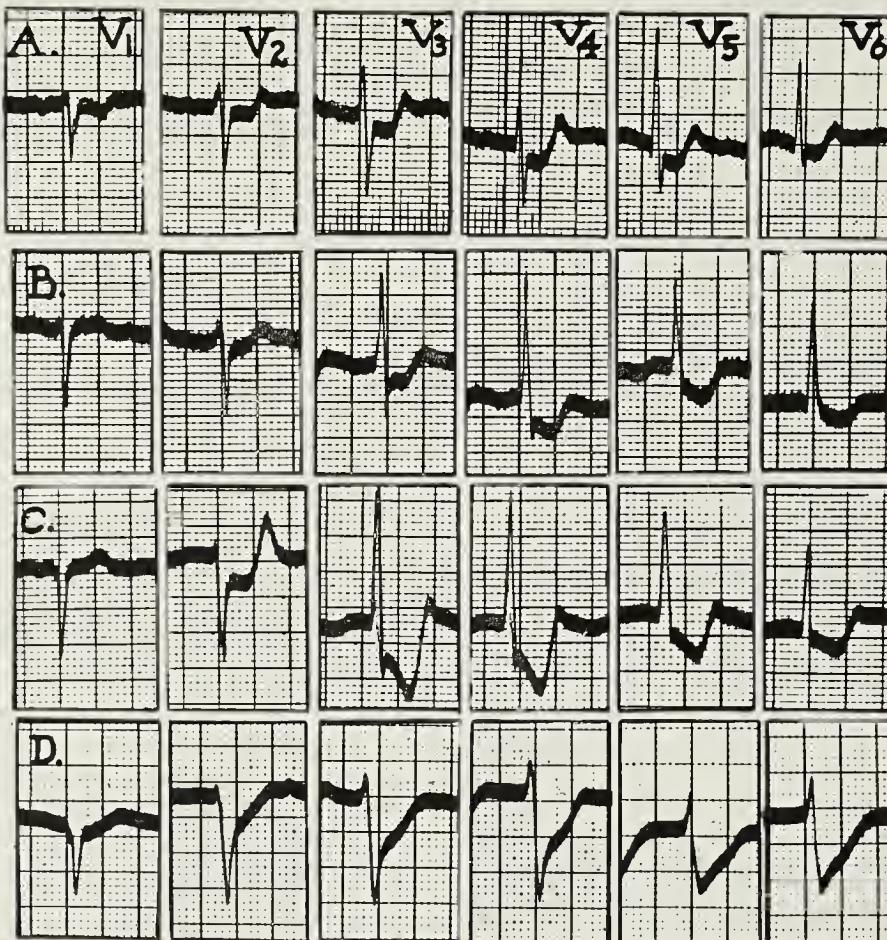


FIG. 75. RST segment and T wave changes suggesting "failure of complete subendoocardial repolarization." All examples demonstrate depression of the RST segment in precordial leads. The terminal portion of T may or may not be upright. (A) Effect of digitalis on the electrocardiogram of a 55-year-old male (note also the relatively short QT interval). (B) Electrocardiographic changes during an attack of angina pectoris in a 91-year-old infirmary inmate. (C) Unusual electrocardiogram during an episode of acute myocardial infarction following an occlusion of the left coronary artery in a subject with extensive pre-existing coronary artery disease. Widespread subendoocardial necrosis was present at autopsy. (D) Severe diphtheritic myocarditis in a 10-year-old child. Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

**SHORTENING OF QT.** This is regularly induced by digitalis therapy (Fig. 75 A) and may be seen in hypercalcemia (hyperparathyroidism).

**Combined Pattern: Myocardial Infarction.** The electrocardiogram obtained during a spontaneous attack of *angina pectoris* may reveal no significant abnormalities or may display T wave changes which are usually, though not always, of the kind illustrated in figure 75. When the resting electrocardiogram shows abnormal T waves, paradoxical reversal may be noted during

**REDUCTION OR DISAPPEARANCE OF R AND INCREASE IN Q WAVES.** This is particularly striking in leads from the free wall of the left ventricle ( $V_5$ ,  $V_6$ ) and constitutes the major cause of "low voltage" of QRS in these leads. As may be seen from the diagram of figure 78, the appearance of a negative deflection of QRS (Q wave) in an epicardial lead may be considered an admixture of the endocardial pattern to the surface electrocardiogram—i.e., it signals the presence of electrically inactive tissues (a scar) between the

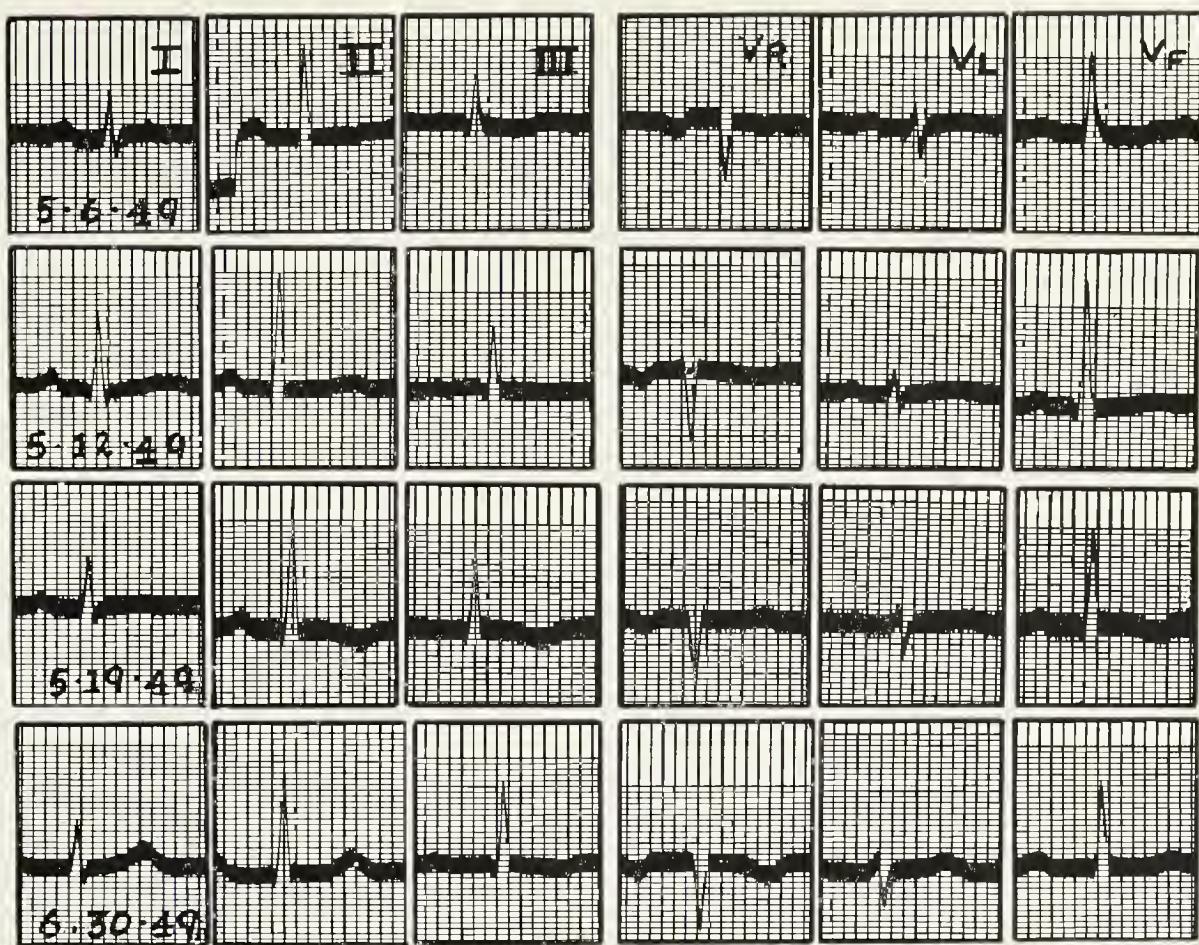


FIG. 76. T wave changes in pericarditis. Serial electrocardiograms of a 25-year-old farmer, who was admitted with signs and symptoms of acute pericarditis. Standard and unipolar limb leads revealed at first only minor changes in T and on 5-19-49 inversion of the final portion of T in leads II, III, and V<sub>f</sub>. The latter reveals slight elevation of the RT junction. Except for a prolonged PR interval, record was normal on 6-30-49. Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 50 mm./sec. (See figure 77.)

inner and the outer surface of the heart. Therefore, once present, an excessive Q wave rarely disappears (fig. 78).

A deep QS deflection of normal width in more than two precordial leads may be taken as presumptive evidence of myocardial scarring, particularly if leads to the left of the sternum are involved. A decrease in the height of R as the electrode is moved across the chest and present prior to the point of transition from the right to the left ventricular pattern should be regarded with suspicion. It is recalled that small Q waves are a normal feature of the electrocardiogram obtained from the left ventricle and in standard bipolar limb leads. Deep QS deflection may be noted in precordial leads over the contralateral ventricle in bundle branch block and in ventricular enlargement. They are the rule in normal right arm leads and in leads from the right upper chest of normal subjects and in subatrial and atrial esophageal leads (endocardial pattern).

**ELEVATION OF RT JUNCTION.** Displacement of this segment may be so striking initially as to obliterate the downstroke of R ("monophasic" response) (fig. 79). The region surrounding the completely inert center of the infarcted segment may be considered to undergo a phase of severe "injury" (necrobiosis). These pericentral areas fail to repolarize completely during diastole and this results in ST segment shifts (fig. 59). RST elevation in precordial leads, in leads from the left arm or left leg, and in standard bipolar limb leads are to be considered as primarily indicating epicardial effects. They are present even if the infarct extends through the entire thickness of the wall, because for these leads the effects of subepicardial regions predominate and the somewhat more remote though perhaps equally striking changes of intramural or subendocardial injury are generally masked by equally striking changes of the epicardial surface.

RST segment changes occur early and are transient because the injured region either re-

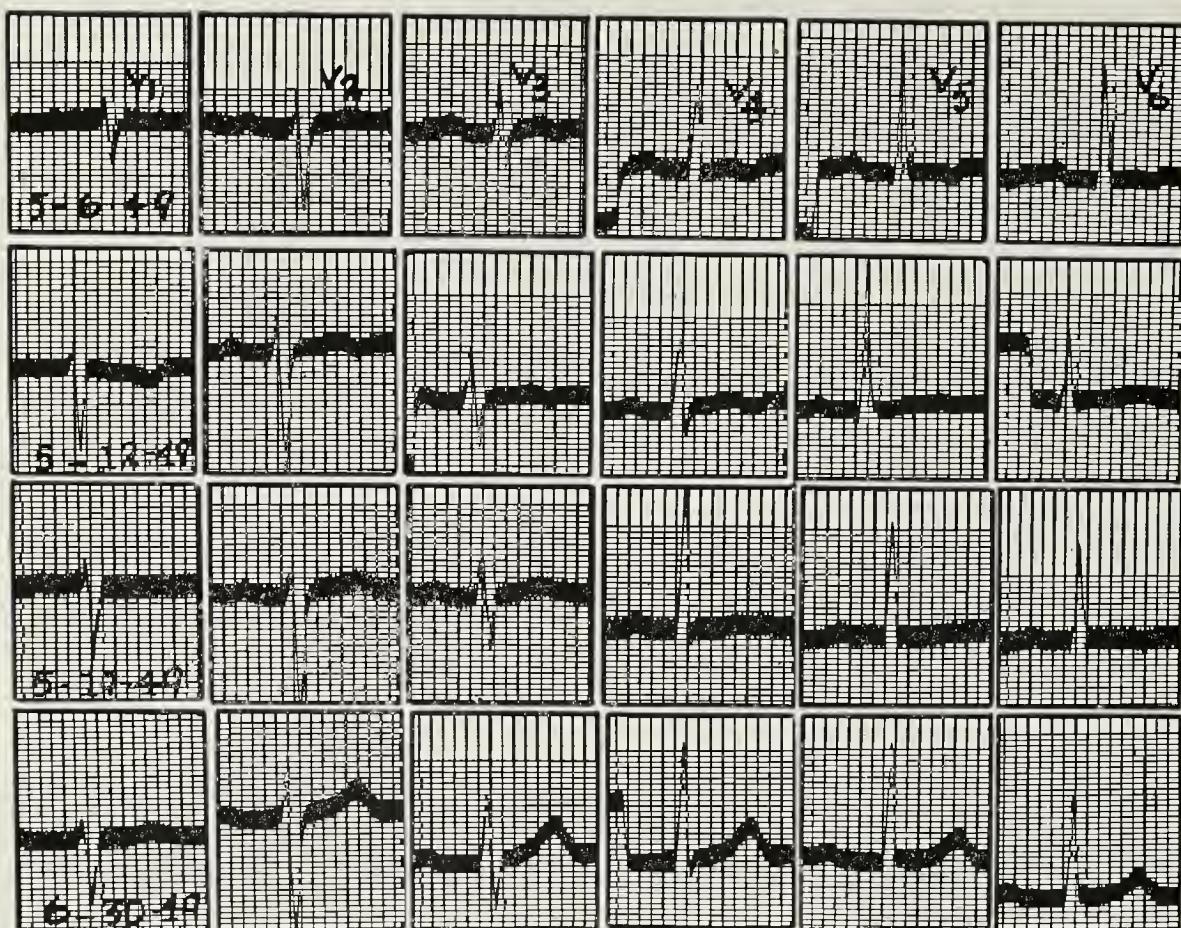


FIG. 77. T wave changes in pericarditis—(Continued).

Serial precordial leads on the patient of figure 76 demonstrate waxing and waning of T wave inversion, first over the left, then over the right precordium. No significant changes were present on 5-19-49 when diaphragmatic involvement was noted in bipolar and unipolar limb leads (fig. 76).

The waxing and waning of T wave changes of the epicardial type, moving from position to position, is not an uncommon finding in pericarditis, but no single tracing allows a definite diagnosis. Elevation of the RT junction is less common and occasionally involves all three standard leads simultaneously.

Time lines: 0.04 and 0.20 second. 10 mm. = 1 mv. Film speed: 50 mm./sec.

covers or becomes incorporated in the electrically inactive scar. In either event, RST segment shifts must disappear. RST segment shifts are usually less striking and tend to disappear earlier

supply without obvious occlusion or with a pinpoint opening of the involved artery may be observed, which gives rise to a state of prolonged angina of chronic coronary insufficiency.

**INVERSION OF TERMINAL PORTION OF T.** Alterations of T may be taken to demonstrate delayed repolarization, and it appears that these changes arise from the margin of an infarcted segment where "injury" is least severe and where a state of mild "ischemia" prevails (figs. 79, 80). In clinical examples inversion of T usually occurs somewhat later (hours or days) than the RST segment shifts and when demarcation has become evident. Since it is the expression of the mildest degree of injury ("ischemia"), it is clear why inversion of the terminal portion of T precedes RST segment displacement and the appearance of Q waves in experimental ligations of coronary arteries (Bayley), and why in the later stages of healing infarction this pattern may be made to

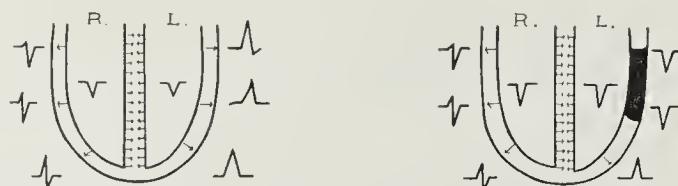


FIG. 78. Origin of Q waves in myocardial infarction. The electrically inert tissue of complete transmural infarction of heart muscle permits a break-through of the endocardial pattern to the outside (see text, p. 380). The left-hand diagram represents a normal, the right-hand diagram an infarcted, heart muscle.

in limb leads than in precordial leads. They generally regress during the second week, although they may last for not more than a few hours or persist for months and years. In the latter case, extremely severe restriction of blood

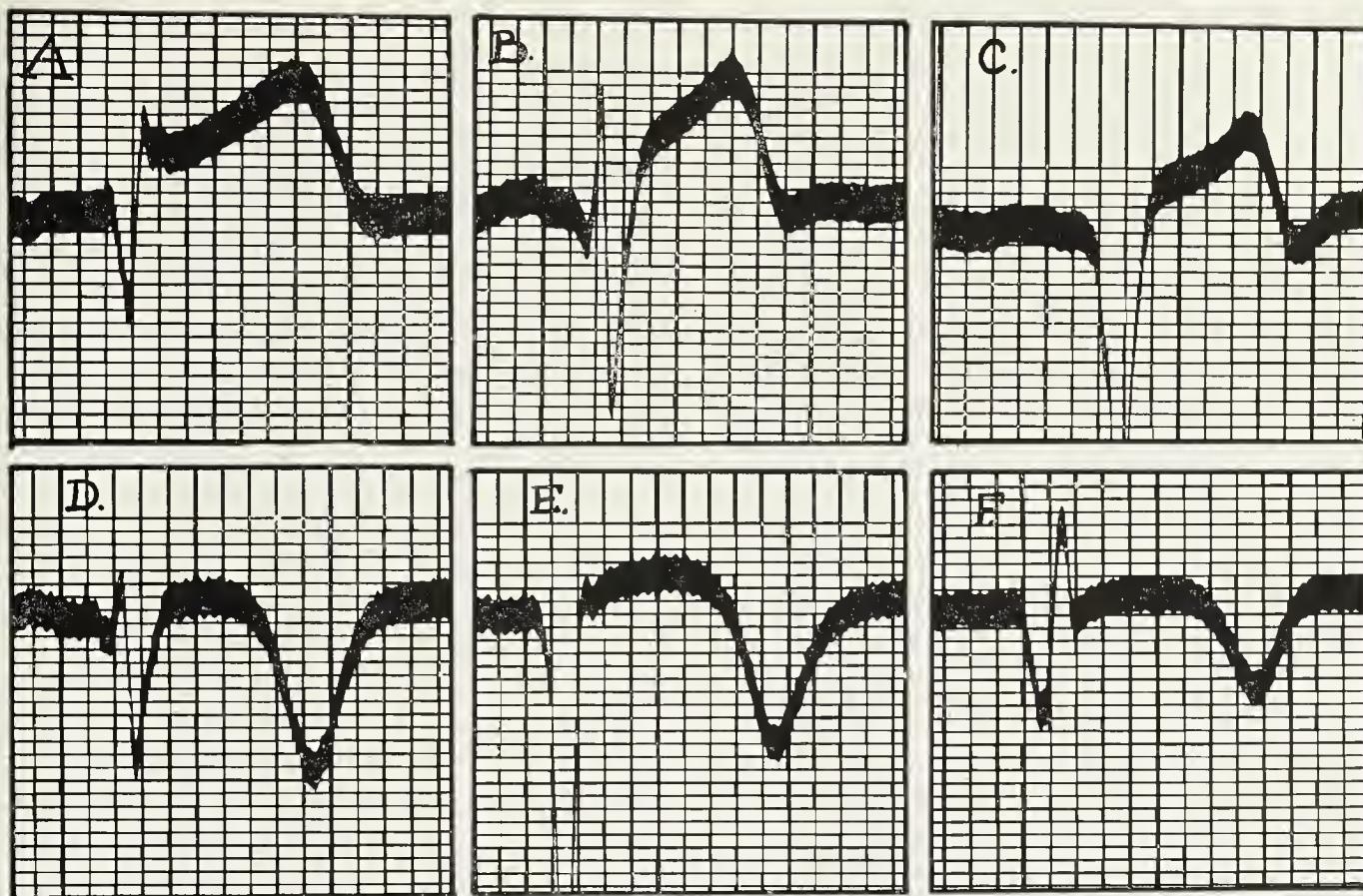


FIG. 79. RST segment shifts and T wave changes in myocardial infarction. Six examples of semidirect leads taken over the infarcted segments. In all, QRS and T wave changes are present.

A and B represent examples of recent infarction with marked displacement of the RT junction and the ST segment. The terminal portion of T has yet remained upright. C represents a somewhat later stage with moderate elevation of RST segment and beginning inversion of T. D and E show the subacute phase with huge inversion of T. F represents a common pattern of old myocardial scarring with deep Q waves and terminal inversion of T, but without ST segment shifts.

Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 50 mm./sec.

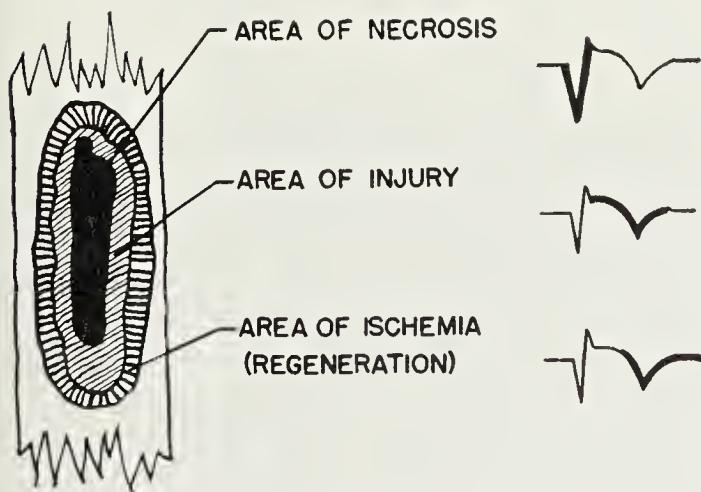


FIG. 80. The origin of electrocardiographic changes in myocardial infarction. The decreasing intensity of the destructive processes of the infarcted region illustrated at the left is correlated with the electrocardiographic pattern on the right. Changes of QRS are the consequence of the central area of necrosis, and they will be present in the surface electrocardiogram if this region reaches the subepicardial layers. The surrounding regions show lesser degrees of ischemia and are responsible for RST segment shifts and T wave changes (see also figure 73). (Courtesy, Hecht: *Arch. Int. Med.*, 84:711, 1949.)

revert to a more acute phase with RST segment displacement upon additional injury such as exercise or the inhalation of low oxygen mixtures. This return to a more acute pattern on exercise in subacute or chronic myocardial infarction may have prognostic significance. A diagrammatic illustration of the three types of changes with respect to the intensity of the injury is given in figure 80.

The diagnosis of myocardial infarction from the electrocardiogram may be further amplified by an admittedly rough estimation of (1) the age, (2) the location, and (3) the size of the lesion.

The estimation of the *age* of the lesion depends on the presence of significant RST segment displacement. It usually decreases in intensity during the first week and in standard limb lead is rarely present in the third week, providing records are obtained during mental and physical rest. In the subacute phase a peculiar deep in-

version of T may appear with voltage of T at times exceeding that of QRS (fig. 80). Such huge T waves have been recorded from the margin of experimental infarction where regenerative changes are particularly active.

The *location* of the lesion obviously influences the appearance of the triad in any given lead. Lesions extending to the left lateral cardiac margin will influence leads I and V<sub>L</sub> (large anterior, anterolateral, and posterolateral lesions). Lesions extending to the diaphragmatic surface will influence leads II, III, and V<sub>F</sub> (large posterior, posterolateral, and posterodiaphragmatic lesions). Straight anterior infarction ("anteroseptal") may be seen only in precordial leads. This is a relatively common type and the one most frequently missed if only standard limb leads are recorded. In straight posterior lesions the triad may be seen only in esophageal leads if the heart is vertically placed. Lesions confined to the higher left cardiac border may appear in lead V<sub>L</sub> only. These "high lateral" infarcts, therefore, may be seen in lead I but will fail to show the characteristic changes in the conventional precordial leads. Occasionally one single episode may involve both the posterodiaphragmatic and anteroapical regions ("anteroposterior" infarcts).

From the standard limb leads alone it is customary to group all posterior infarctions (usually caused by occlusions of the circumflex branch of the right coronary artery) as a QIII TIII pattern, and all anterolateral lesions (usually caused by obstructions of the descending branch of the left coronary artery) as QITI pattern. Lateral infarcts (circumflex branch of the left coronary artery), multiple infarcts, and posterior infarcts in horizontally placed hearts may result in mixed types (TIQIII) patterns, the nature of which can usually be clarified by further supplementary electrocardiographic exploration.

The *size* of the infarcted segment may be estimated roughly from the number of semidirect leads involved in QRS changes.

Multiple myocardial infarcts so common pathologically are difficult to recognize without serial examinations because remote effects of one infarcted region may tend to obliterate the telltale signs of others. The diagnosis may be simple if repeated examinations are available. In general, the latest lesion takes precedence over the preceding ones, and it is rarely possible to recog-

nize more than two episodes from the electrocardiogram.

*Infarcts complicated by bundle branch block* may lack the typical triad because the striking alterations caused by the conduction defect may mask relatively minor changes induced by the infarcted region. In right bundle branch block, Q waves may be seen in semidirect leads taken from the infarcted region. In left bundle branch block where the left ventricular cavity remains positive throughout a major portion of the cardiac cycle (fig. 58), Q waves cannot be expected to occur and a diagnosis of infarction, particularly during later stages when RST segment changes have cleared, may be impossible. It is unwise to exclude myocardial infarction in the presence of bundle branch block (fig. 81).

Occasionally, clinically typical episodes fail to develop the characteristic QRS changes and reveal only waxing and waning of T waves even if a number of precordial leads have been employed. It is assumed that no endocardial admixture has occurred, because the infarcted region has not extended through the entire ventricular wall. Only a relatively slightly injured ("ischemic") region faces the exploring electrode. Such patterns are now tentatively labeled as "nonpenetrating" infarcts. If occlusion of a coronary artery develops in a heart that has undergone previous episodes of complete occlusion or has suffered from the effects of widespread narrowing of the vascular bed, the new injury may result in very extensive necrosis of subendocardial layers. The electrocardiograms may then show striking depression rather than elevation of the RST segment ("injury in reverse"—Bayley). An example of these prognostically poor "subendocardial" infarctions has been illustrated in figure 75.

The later stages of myocardial infarction are characterized by a gradual resolution of RST segment shift and a tendency of T to return to a normal pattern. QRS complexes may remain unchanged. If T remains inverted, the electrocardiogram obtained several years after the insult may be indistinguishable from a record obtained only two or three weeks following the acute episode. If T returns to normal and Q waves do not develop (nonpenetrating type), the electrocardiogram may return to a completely normal pattern. The absence of electrocardiographic findings, therefore, does not exclude the presence of a myocardial scar.

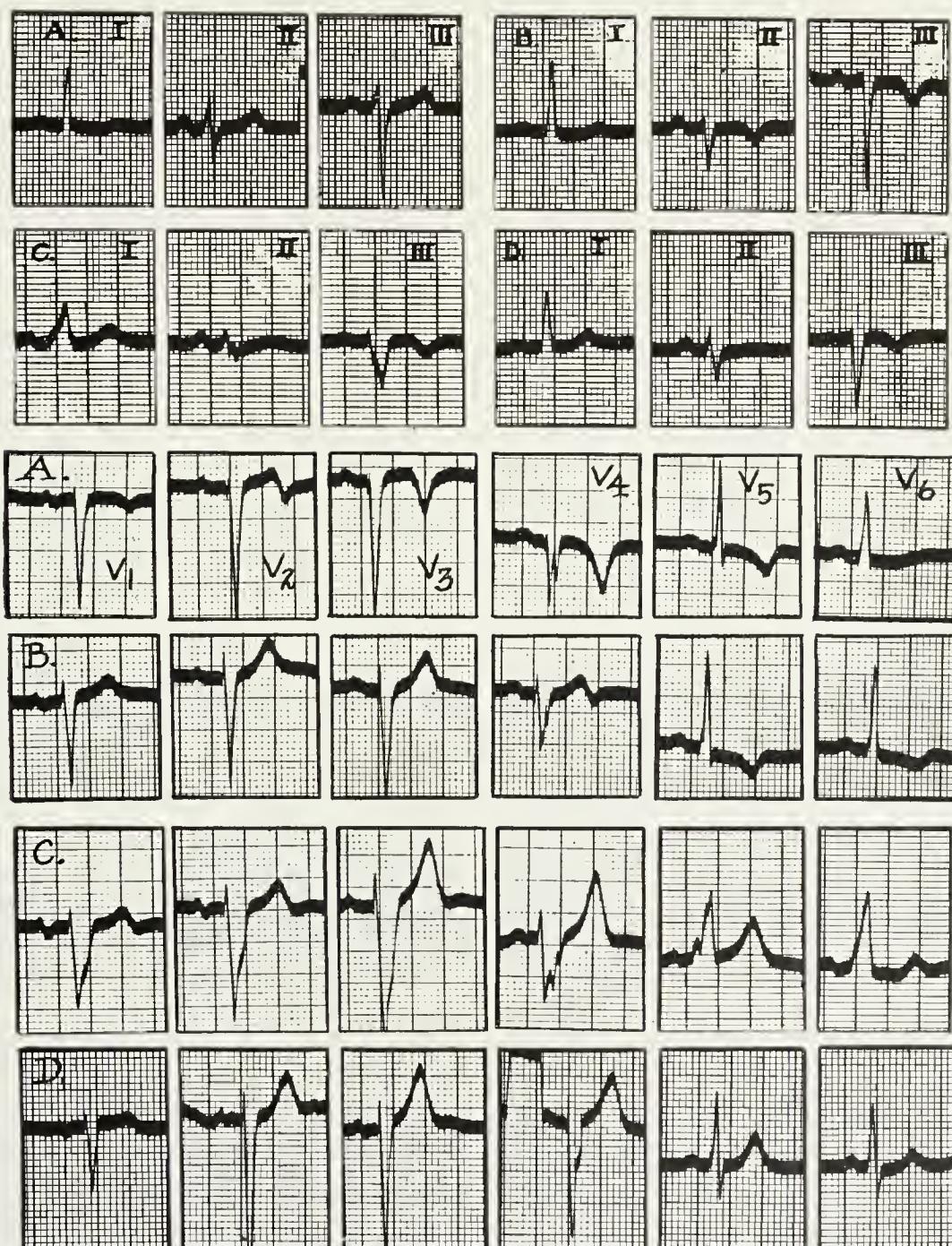


FIG. 81. Multiple myoedrial infarction and bundle branch block. Serial records of a 76-year-old laborer who had suffered an attack of coronary occlusion in 1942 and re-entered the hospital on 12-11-48 (A). At this time standard limb leads were compatible with left ventricular enlargement but precordial leads revealed the presence of a straight anterior myoedrial scar.

Another episode of intense preeordial pain occurred on 12-12-48. On 12-13 (B) standard leads revealed decrease in size of R and sharp terminal inversion of T in II and III. Preeordial leads demonstrated a return of Q in V<sub>2</sub> to V<sub>4</sub> and complete reversal of the previously inverted T wave. (Note: Paradoxic reversal of T and QRS changes completely obliterated the signs of previous infarction.)

During the course of the next few days the patient developed left bundle branch block (C). The conduction defect so altered the record that neither the old nor the recent infarction remained recognizable and in later records (D) only vestiges of the recent diaphragmatic (T wave changes in III) and the old anterior infarction (diminutive Q waves in V<sub>2</sub>-V<sub>4</sub>) remained.

The records demonstrate the value of serial electrocardiographic examinations and point to the limitations of clinical electrocardiography: a negative electrocardiographic finding does not rule out a clinical diagnosis.

Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

**Combined Pattern: Ventricular Enlargement.** Predominantly one-sided ventricular enlargement results in a number of electrocardiographic changes that may appear singly or in combination, depending largely on the degree of involvement and the rotation of the heart occasioned by the increase in ventricular mass. When enlargement is definite, electrocardiograms are characterized by:

1. Delay in the onset of the intrinsicoid deflection over the involved ventricle (figs. 57, 82, 83, 84, table 38).
2. Increase in the size of the preintrinsicoid upward deflection (R) over the involved ventricle and of the postintrinsicoid downward deflection (S) over the contralateral side (figs. 57, 58, 82, 83).

3. Depression of the RST junction and inversion of the terminal segment of T over the enlarged ventricle. The final ventricular deflection assumes a characteristic shape that is only rarely mimicked by other abnormalities (figs. 73g, 82, 83, 86).
4. A concomitant change, generally overstressed, involving the deviation of the modal electrical axis of QRS which demonstrates relatively pronounced "left axis deviation" in left, and "right axis deviation" in right, ventricular enlargement. There are many exceptions to this rule (figs. 64, 66, 82).

If dilatation is excessive, the enlargement pattern may glide into one denoting defects in intra-

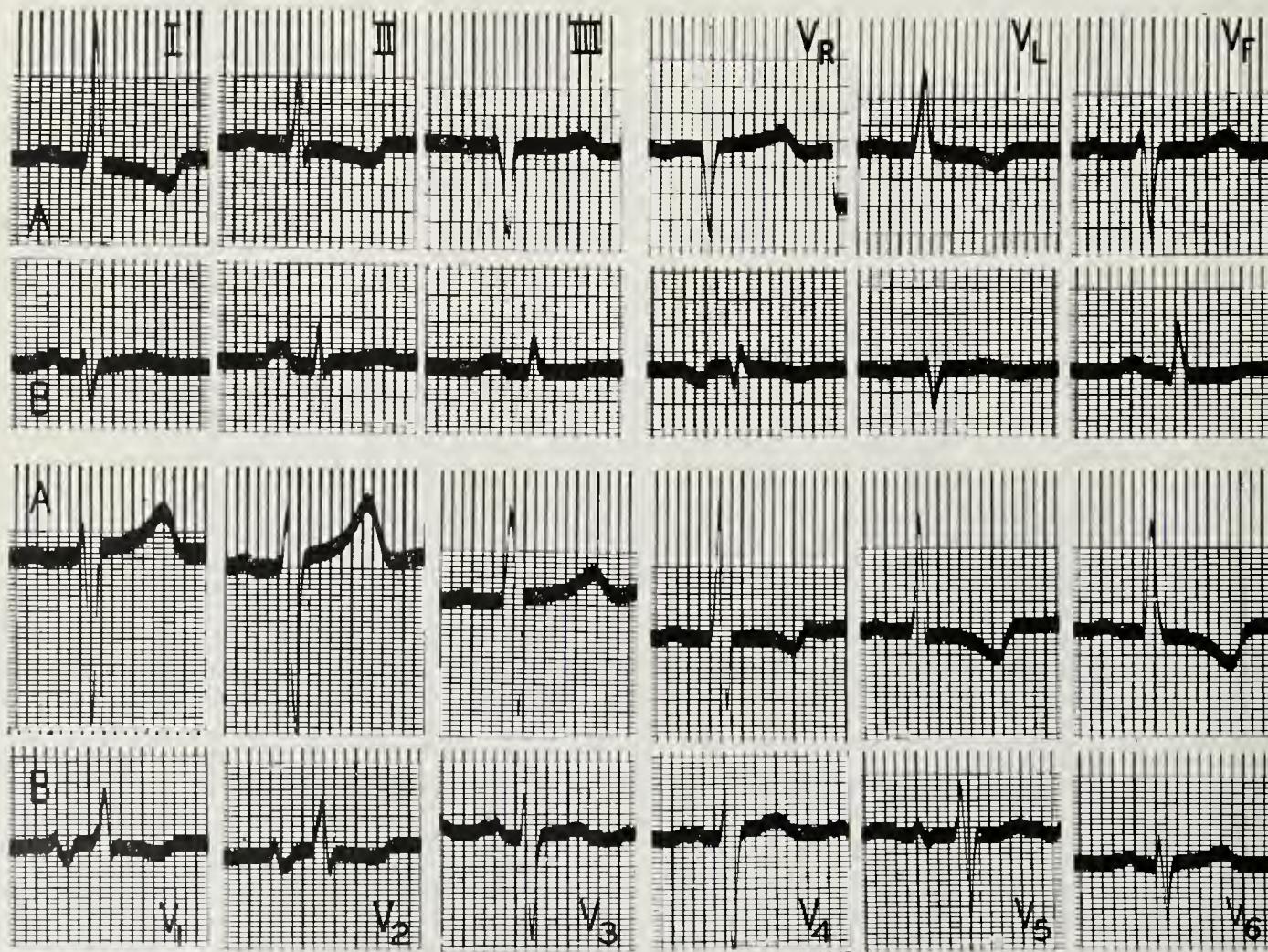


FIG. 82. Ventricular enlargement.

(A) Left ventricular enlargement in a horizontally placed heart. Note "left axis deviation" of QRS in standard limb leads, large deflections in precordial leads, slight delay of intrinsicoid deflection over the left ventricle ( $V_5$  and  $V_6$ ), and inversion of the terminal portion of T in I, II,  $V_L$ ,  $V_5$ , and  $V_6$ . The subject is a 66-year-old housewife with essential hypertension and hypertensive heart disease.

(B) Right ventricular enlargement in a vertically placed heart. Note "right axis deviation" of QRS in standard limb leads, large biphasic QRS deflection in midprecordial leads (not always present), definite delay of intrinsicoid deflection with upright R and terminal inversion of T over the right ventricle ( $V_1$  and  $V_2$ ). The presence of "mitral P waves" (see figure 68) suggests left auricular enlargement. The subject is a 26-year-old linotype operator with advanced mitral stenosis.

Time lines: 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

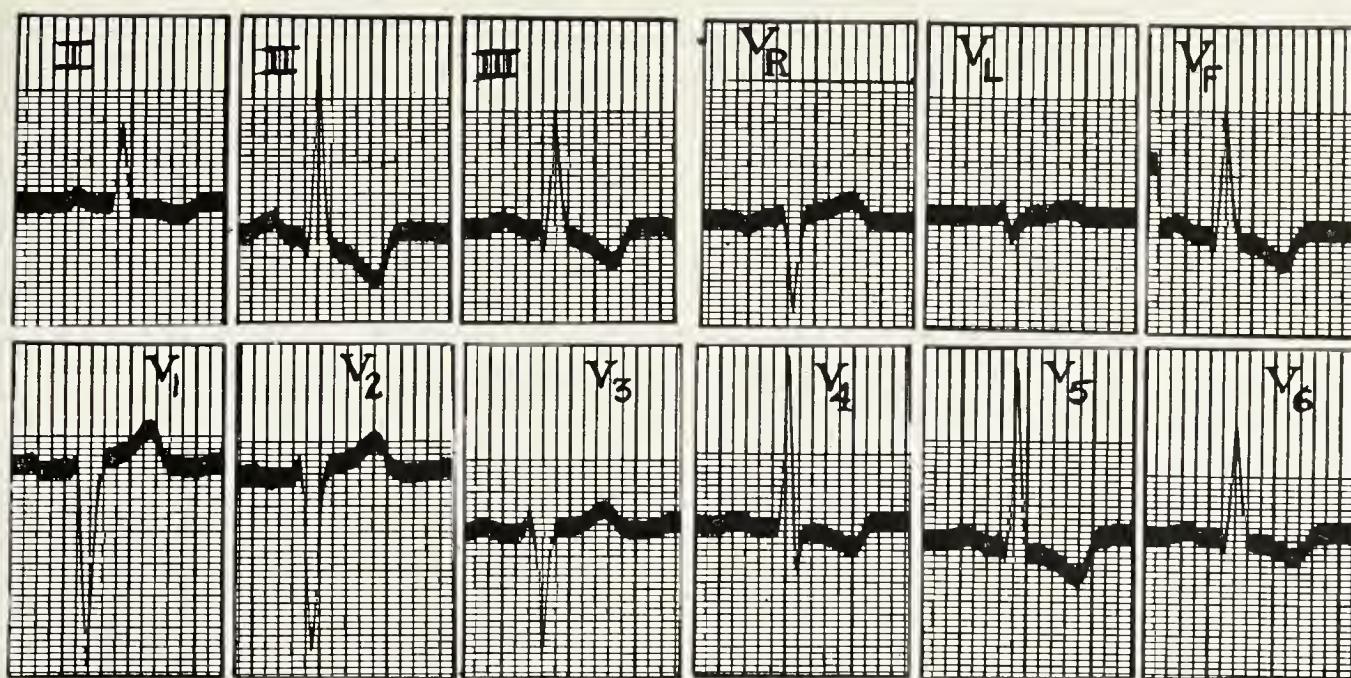


FIG. 83. Left ventricular enlargement in a vertically placed heart (see also fig. 86).

The findings are those of A of figure 81 (A) except that the left ventricular pattern is seen in  $V_f$  instead of  $V_L$ . There is no left axis deviation, and T wave changes occur in II and III. Inversion of T in I is caused by an abnormal  $V_R$  lead and is not directly comparable to the T wave changes in lead I of figure 81 (A).

The subject is an asthenic veteran, age 53, with advanced aortic stenosis on the basis of rheumatic heart disease.

Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 50 mm./sec.

ventricular conduction with patterns resembling, but usually not identical with, those of left bundle branch block in left ventricular enlargement and those of right bundle branch block in right ventricular enlargement.

It is easily understood that a certain delay in the onset of the intrinsicoid deflection should accompany an increase in the size of the free wall of the enlarged ventricle and that this will also account for a certain increase in width of QRS and in the size of the R wave (fig. 58). Marked increase in the mass of the activated muscle easily accounts for a decrease of R with an apparent earlier onset of the intrinsicoid deflection over the contralateral ventricle. These are remote effects of activation of distant regions upon a semidirectly recording electrode. The practice of estimating the intrinsicoid deflection and, from this, drawing conclusions on the time of arrival of the impulse subjacent to the recording electrode therefore becomes invalid over the contralateral ventricle in ventricular preponderance and, for the same reason, in bundle branch block.

The high voltage of the preintrinsic upright deflection over the involved side cannot, however, be explained solely by a delayed arrival of the impulse at epicardial layers. An increase in the number of activated muscle fibers may be re-

sponsible. Potassium administration generally and temporarily reduces excessive high voltage in these cases.

Changes in the final deflection occur during the later stages of enlargement (Figs. 82, 83). Only to a minor degree are these secondary to changes induced by the increased area of QRS (secondary T wave changes). They are mainly of the primary type and, from what has been said, these changes may be considered as a combination of more distant, presumably subendocardial failure of complete diastolic repolarization (depression of RT junction) and of subepicardial repolarization delay (inversion of terminal segment of T). The electrical response of subendocardial layers appears more severely altered than that of outside regions, and increasing one at the expense of the other may readily accentuate either RST depression and the ST segment, or the T wave proper, depending perhaps on the ease by which different layers may respond to superimposed stresses such as anoxia or potassium administration. The characteristic shape of the final ventricular deflection in ventricular enlargement may therefore be altered by the co-existence of additional factors such as myocardial ischemia or digitalis administration. The presence of primary T wave changes points to changes that are initiated by but that are not

essential to ventricular hypertrophy. The term *ventricular strain* should be reserved for records that display such changes of the final ventricular deflection to a marked degree.

Left axis deviation of QRS may be considered the result of rotation of the heart on its longitudinal axis with the left ventricle assuming a marginal position and the left ventricular pattern shifting from its normal position of  $V_F$  to  $V_L$ . Left ventricular enlargement with classic changes in semidirect leads may occur without it (figs. 83, 84). On the other hand, rotation need not occur to provide right axis deviation in right ventricular enlargement. Even in a horizontally placed heart, right axis deviation will appear if, due to the hypertrophy of the right ventricle, the right ventricular pattern is made to resemble the normal left (Q wave, tall R) (fig. 57) and the left ven-

tricular pattern is made to resemble the normal right (absent Q, deep S). More commonly, the heart remains in the normal vertical position and the enlarged right ventricle contributes little to the extremity leads.  $V_F$  displays either the usual left ventricular pattern or a combination of the abnormal right and the normal left ventricular form. The pattern of  $V_L$  in such instances represents the potential variations of a relatively unchanged pulmonary conus.

The signs of left ventricular enlargement correlate well with clinical and pathologic instances of left ventricular hypertrophy. Dilatation of the right ventricle and right ventricular hypertrophy is not always detectable in semidirect leads, though right axis deviation of the modal axis of QRS in standard leads is generally present. At

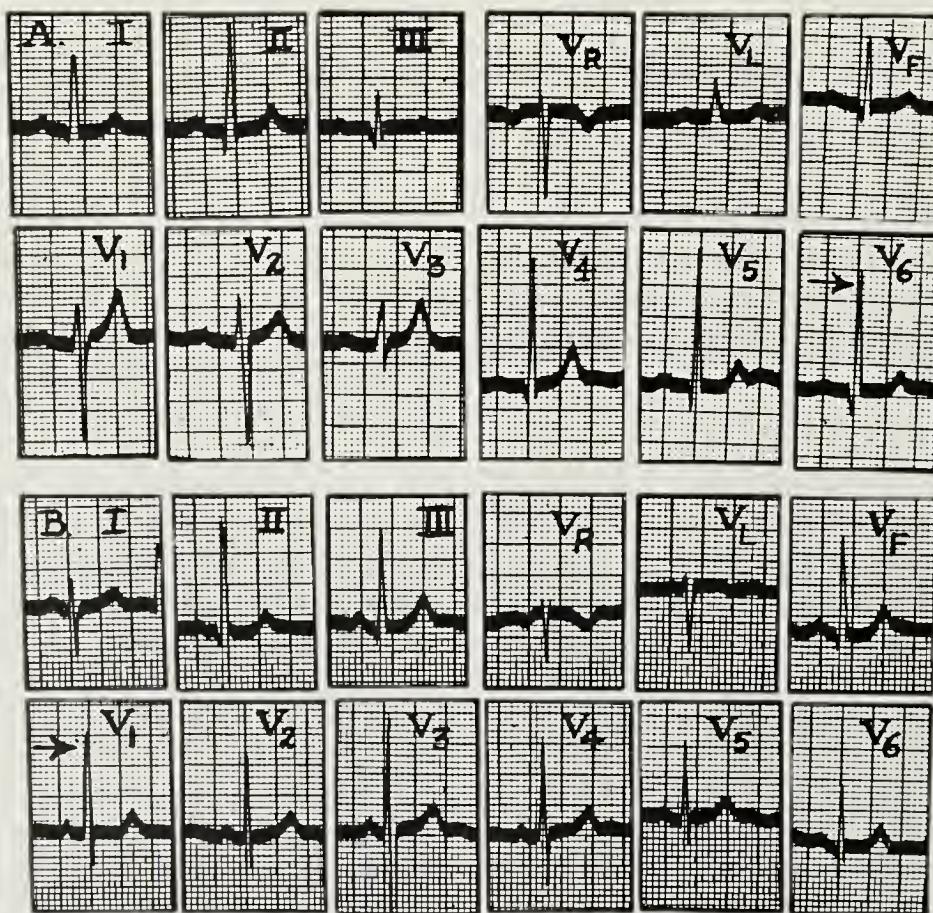


FIG. 84. Ventricular enlargement: diagnosis established by pectoral leads only.

(A) A 28-year-old typist with classic aortic insufficiency (rheumatic heart disease). The electrocardiogram appears normal, but a definite delay of the intrinsieoid deflection over the left ventricle is present (peak of R 0.65 second after beginning of QRS: arrow). This is an unequivocal sign of left ventricular hypertrophy in the absence of demonstrable conduction defects.

(B) A 21-year-old farm girl who displayed a loud systolic murmur along the left sternal border but had no other physical signs. A right axis deviation of the standard limb lead electrocardiogram was considered to be compatible with the patient's physical stature, but pectoral leads over the right ventricle demonstrated definite evidence of right ventricular hypertrophy (late intrinsieoid deflection with upright R in  $V_1-V_3$ : arrow) with unusually large deflections over the midprecordium. Further investigation revealed slight arterial unsaturation, and cardiac catheterization then demonstrated the presence of a congenital lesion of the tetralogy of Fallot variety.

Time lines: 0.20 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

times only transient T wave changes occur in right-sided chest leads or in V<sub>F</sub> (and in consequence in leads II and III); at other times the precordial electrocardiogram remains essentially normal. This is of particular concern in the diagnosis of acute *pulmonary embolism* or in exacerbations with acute right-sided dilatation of chronic cor pulmonale. Sudden right axis deviation or even the occurrence of right bundle branch block with or without the QRS and T wave change of right ventricular enlargement, in a patient with an acute illness accompanied by tachycardia and chest pain, suggests acute dilatation of the right ventricle occasioned by massive pulmonary embolism. Serial electrocardiographic examinations are of particular value, as these changes occur instantaneously and as a rule may not persist for

more than a few hours or days unless chronic cor pulmonale develops. (See figure 3, p. 25.)

#### Combined Pattern: Electrolyte Disturbances.

During the last decade the electrocardiogram has become a valuable indicator of a number of electrolyte disturbances occurring in the absence of demonstrable cardiac disease. Chemical detection of such changes may be incomplete or difficult, but the correlation has now been carried far enough to suggest an electrocardiographic examination as a clinical guide in subjects in and emerging from diabetic coma, in cirrhosis of the liver, in acute and chronic nephritis with and without hypertension, in Addisonian crisis, in severe nutritional deficiencies, in hyperparathyroidism and hypoparathyroidism, in tetany, and in familial periodic paralysis.

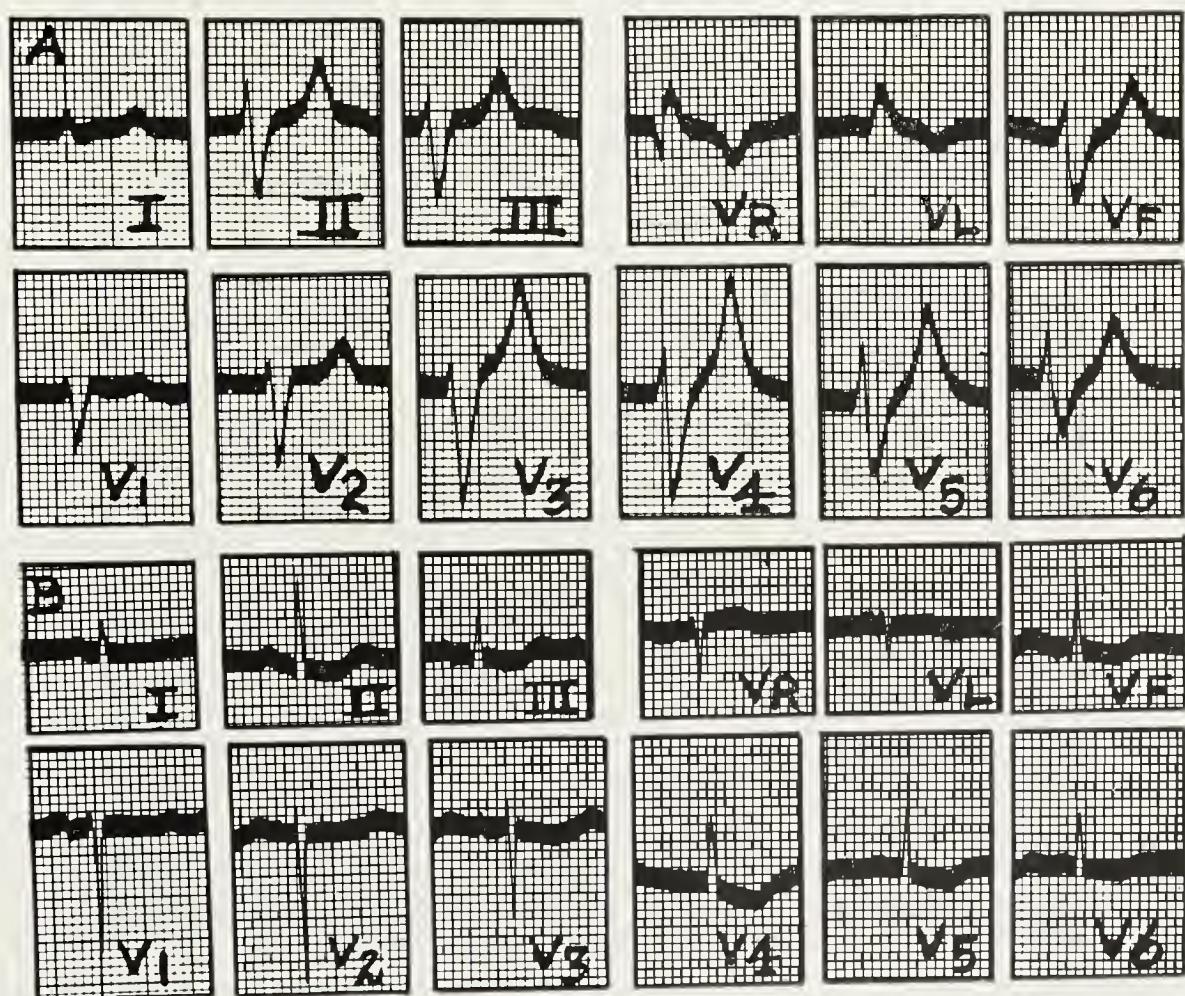


FIG. 85. Electrolyte imbalance: hyper- and hypokalemia.

(A) Record of a 28-year-old veteran, one day prior to death from uremia (glomerulonephritis). *Electrolyte pattern:* high potassium, calcium, and phosphates; low sodium (K: 8.23 mEq./l.; Na: 129.6 mEq./l.; Ca: 12 mg. %; PO<sub>4</sub>: 19 mg. %); B.U.N.: 400 mg. %; uric acid: 9.6 mg. %; creatinine: 19.2 mg. %. (Note: Bizarre ventricular complexes with absence of P waves [auricular paralysis]. QRS 0.13 second, T waves tall and spiky. Pronounced U waves in II and conduction [general depression of conductivity].)

(B) Record of a 55-year-old veteran, obtained during recovery from diabetic coma. *Electrolyte pattern:* Low potassium, normal sodium (K: 2.6 mEq./l.; Na: 150 mEq./l.); glucose: 780 mg. %; CO<sub>2</sub> combining power: 42 vol. %; B.U.N.: 70 mg. %. (Note: Depression of RST segment with flat, positive T waves; long QT interval seen best in V<sub>1</sub>-V<sub>3</sub>. The heart appears vertically placed.)

Time lines: 0.04 and 0.2 second. 10 mm. = 1 mv. Film speed: 25 mm./sec.

*Hypercalcemia and hypocalcemia* in diseases of the parathyroid glands, and severe alkalosis in chronic nephritis may result in shortening or lengthening of the total electrical systole without additional electrocardiographic changes (see p. 379).

*Hyperkalemia* (hyperpotassemia) causes a characteristic change as soon as the serum potassium level more than doubles (figs. 85, 86). The changes consist of a reduction in voltage of QRS with widening of the entire ventricular complex and involving both QRS and T. In contrast to bundle branch block, there is no unilateral delay in conduction in semidirect leads. The QT interval increases, but, in contrast to calcium deficiency, this is associated with profound altera-

tions of the electrocardiographic complexes. The pattern is readily seen following administration of potassium by mouth, and in the end stages of chronic glomerulonephritis (figs. 85, 86). It may occur early in diabetic coma before treatment has been instituted, and it is presumably the cause of the profound changes of the *pre-terminal electrocardiogram* when beginning dissolution of cells allows the escape of potassium into the circulation. Serum sodium levels are usually, but not always, low.

Potassium causes failure of cells to repolarize completely, and it is therefore not surprising that the early changes are confined to alterations of T. A previously inverted T wave may become

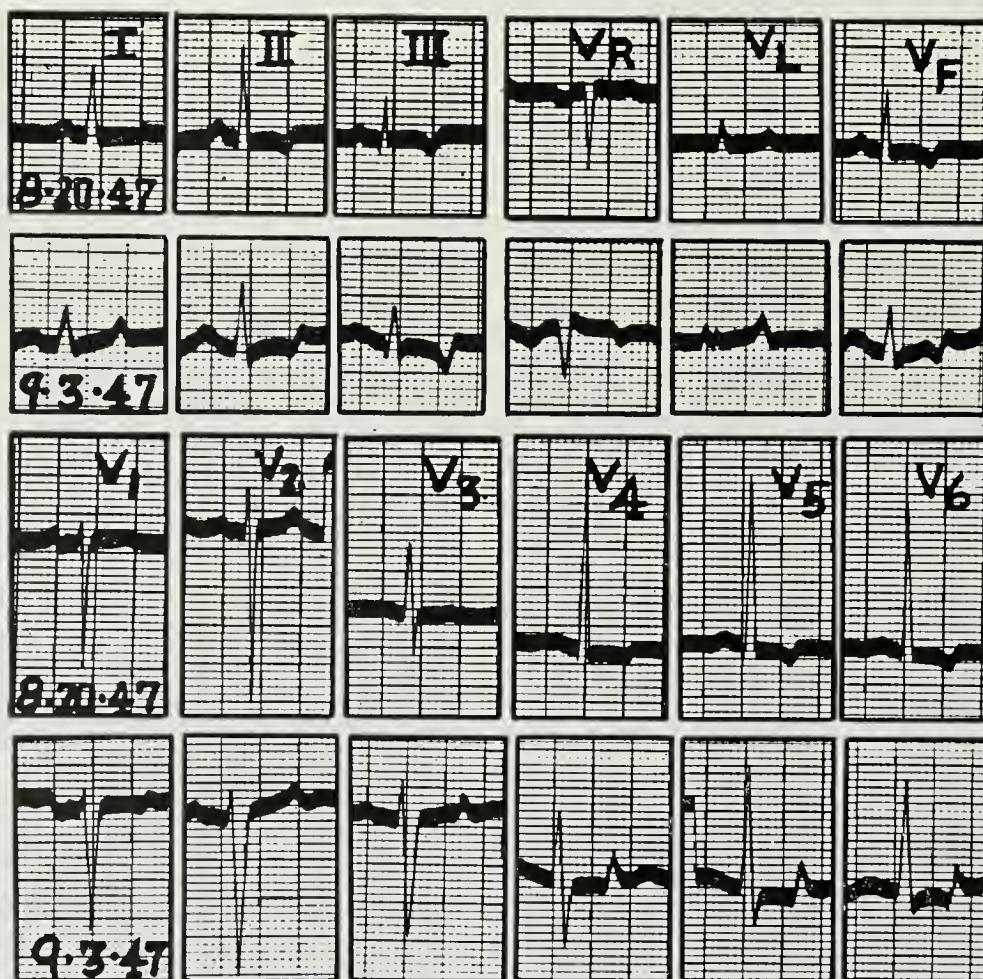


FIG. 86. The electrocardiogram in uremia. Records obtained on a 10-year old-child dying from chronic glomerulonephritis, with hypertensive heart disease, uremia, and pericarditis.

On 8-20-47 the record suggests left ventricular enlargement in a vertically placed heart as demonstrated by the large deflection in precordial leads and the inversion of the final portion of T in II, III, V<sub>F</sub>, V<sub>4</sub>-V<sub>6</sub>. It is doubtful but possible that the uremic pericarditis may have resulted in some of the T wave changes. On 9-3-47, five days prior to death, the PR and QT intervals have increased. The QRS complexes have decreased in size and have widened to 0.11 second without evidence of unilateral conduction delay in precordial leads. The T waves have become abnormally peaked and have changed their direction in leads obtained over the left ventricle (paradoxic reversal). These changes are diagnostic of early hyperkalemia.

There was no exertion of phenolsulfonphthalein in two hours; B.U.N. varied between 52 and 140 mg. %; no electrolyte determinations were performed.

Time lines: 0.2 second, 10 mm. = 1 mv. Film speed: 25 mm. sec.

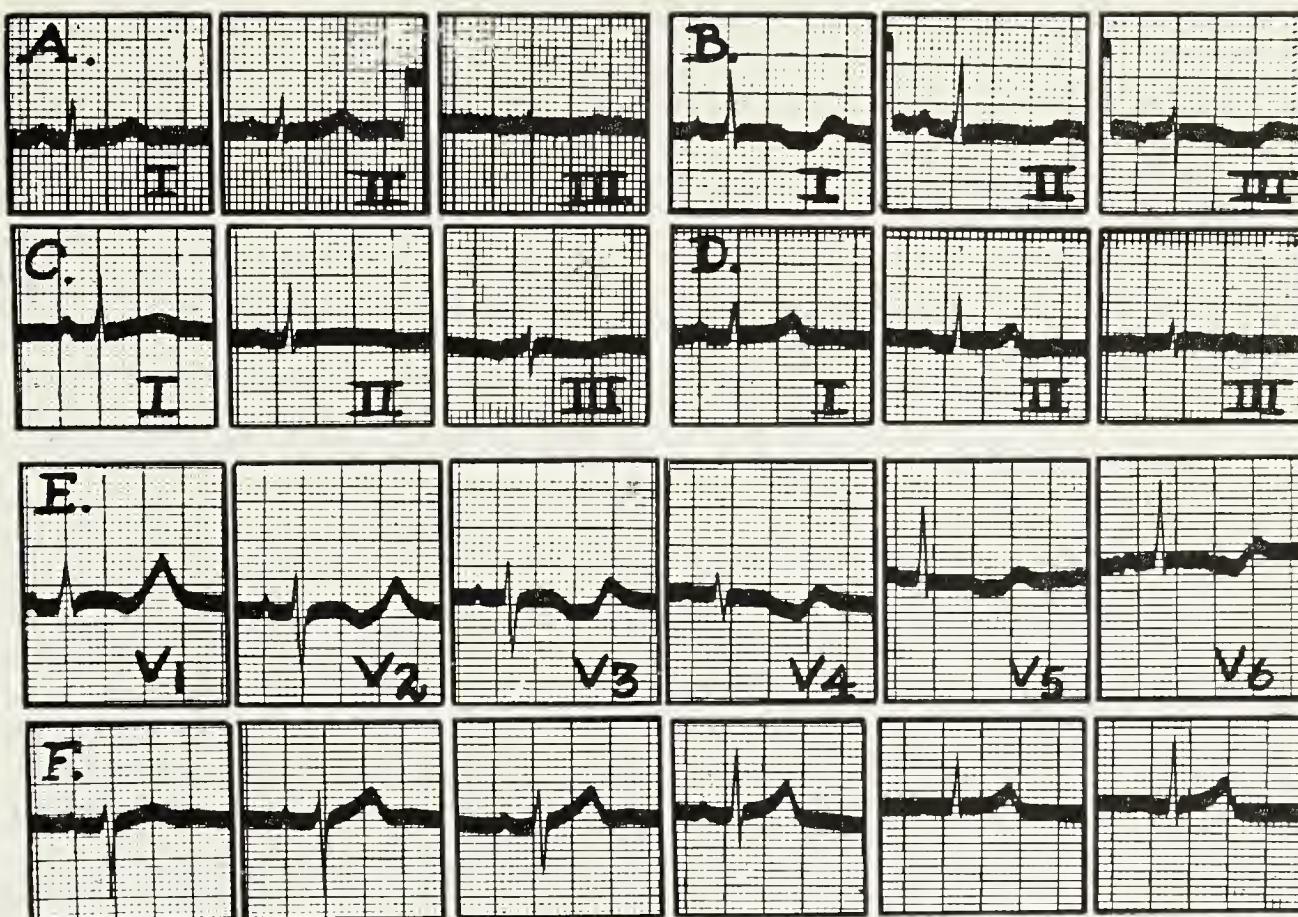


FIG. 87. Multiple electrolyte imbalance. Record of a 38-year-old housewife with lower nephron syndrome following calomel poisoning.

*Electrolyte pattern:* (A) (9-30-48) Acidosis and hyperphosphatemia (K: 5.2 mEq./l.; Na: 116 mEq./l.; P: 11.6 mg. %; B.U.N.: 235; CO<sub>2</sub> combining power: 24 vol. %). (B, E) Hypokalemia and hypocalcemia (K: 1.70 mEq./l.; Na: 144 mEq./l.; Cl: 570 mg. %; Ca: 8.2 mg. %; P: 5.4 mg. %; B.U.N.: 45; CO<sub>2</sub> combining power: 41 vol. %); intravenous calcium gluconate failed to alter the electrocardiographic tracing. (C) (10-16-48) The day following potassium administration by mouth. (D, F) (10-22-48) Recovery: normal electrolyte pattern and normal electrocardiogram (K: 5.15 mEq./l.; Na: 140 mEq./l.; Cl: 630 mg. %; Ca: 8.7 mg. %; P: 4.8 mg. %; B.U.N.: 14; CO<sub>2</sub> combining power: 50 vol. %). The changes are best related to hypokalemia. Alterations in phosphates, calcium, and sodium, and changes in pH and nitrogen retention apparently caused few if any electrocardiographic changes in this patient, and recovery of the electrocardiographic findings occurred promptly upon institution of potassium therapy.

upright (paradoxic reversal) or may become more sharply inverted, depending on the myocardial region most sensitive to change. No alteration of the final deflection will occur if all sections of heart muscle respond to potassium with equal intensity.

A quinidine-like effect of potassium on conduction velocity and impulse formation may cause blocking of abnormal atrial and ventricular foci, and suppression of the sinus node with ventricular escapes and nodal rhythms.

*Hypokalemia* (hypopotassemia), such as is seen in recovery from diabetic coma or from Addisonian crisis, in familial periodic paralysis, or in excessive hydration, appears to cause a transient reversal of the terminal portion of T or depression of the RST segment. These changes are obviously far less characteristic than those

attributed to hyperkalemia, and concomitant alterations of other electrolytes (phosphates, magnesium) have not been excluded (fig. 85).

*Mixed patterns* in examples of profound electrolyte changes such as may be seen in severe sprue, in renal disease, and in hepatic coma are less well understood (fig. 87). The general characteristics of such electrocardiograms suggest fundamental disturbances in membrane charges that are foreign to those obtained in diseases of the heart.

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#### APPENDIX: ELECTROENCEPHALOGRAPHY

Electroencephalography (EEG) bears a resemblance to electrocardiography (ECG) in that electrical potentials of excited tissue transmitted to the surface of the body by volume conduction are picked up by electrodes, amplified, and recorded. The electrocardiogram is basically simpler because heart muscle fibers represent a syncytial system in which the various regions depolarize in a comparatively reasonable order. The brain, however, consists of about  $10^{10}$  neurons arranged in layers, regions, nuclei, and lobes with numerous interconnections, tracts, and commissures in which the various neurons fire in a much more complex fashion.

Detailed knowledge of the genesis of the EEG is scanty, and widely divergent views exist. A brief summary of the observed facts may serve as an introduction, and the works of Toman and Davis, Gibbs and Gibbs, Penfield and Erickson, cited in the References, may be consulted for a more detailed presentation of the subject.

**EEG Record.** The EEG is usually recorded by a multiple-channel device from electrodes placed over the surface of the head. A typical record shows continuous and somewhat rhythmic fluctuations of electrical potential over various areas of the head, approximately one-tenth the size of a standard limb lead electrocardiogram. These fluctuations or "brain waves" constitute the EEG.

A normal record consists of a complex series of waves of various frequencies and amplitudes, of which the following major groups may be distinguished:

1. The alpha rhythm is the most prominent feature of a normal EEG. It consists of sinusoidal waves with a modal frequency of 10 per second and may vary in different individuals from 8 to 12 per second. It arises in the occipital lobe,

sweeps forward, and may in some instances be found as far forward as the frontal region. The alpha rhythm varies in the per cent of time that it occurs from one person to another, and records may be classified as high or low alpha types (fig. 88 B, C, D, F, G).

~~2.~~ Beta activity refers to rhythms of 18 to 25 per second (fig. 88 C). Some prefer the designation "fast waves," with a specification as to the observed frequencies. Beta activity is particularly prominent in frontal and parietal regions of normal records.

~~3.~~ Slow waves of less than 8 per second are found to a certain extent in normal records (fig. 88 A, H, I, J). In abnormal states and during sleep, slow rhythms may predominate. High-voltage slow activity of 4 per second has been termed "delta waves."

**Factors Affecting EEG Pattern.** Various physiologic factors and pathologic states affect the pattern of the EEG. A few of these are particularly noteworthy.

**AGE.** At birth the EEG consists of high-amplitude, irregular slow waves, 0.5 to 3 per second and a small amount of low-voltage fast activity. With increase in age (fig. 88 A, B, C) the basic frequency rises and the waves become more regular. Alpha rhythm appears at the age of 4 to 5, but an adult pattern of 8 to 12 per second combined with beta activity is not fully attained until about 17 to 18 years of age.

**PATTERN VISION.** (Fig. 88 F.) The presence of pattern vision profoundly affects alpha activity. With the eyes closed, the alpha rhythm is present. With the eyes open and focused, the 10 per second rhythm disappears and fast frequencies of low amplitudes may now be noted. Concentration also depresses alpha activity.

**SLEEP.** (Fig. 88 G, H, I, J.) In sleep the whole EEG pattern changes. Slow waves of 3 per second or less appear, accompanied by bursts of about 14 per second waves, the "sleep spindles."

**PHYSIOLOGIC STATES AND PHARMACOLOGIC AGENTS.** The pattern of an EEG is dependent, among other factors, on cerebral blood flow, oxygen tension, the blood sugar level, and the blood carbon dioxide content. Subnormal values of these determinants generally increase slow wave activity of the EEG. As an example, forced hyperventilation with consequent lowering of carbon dioxide tension favors the appearance of slow waves. Preexisting abnormalities

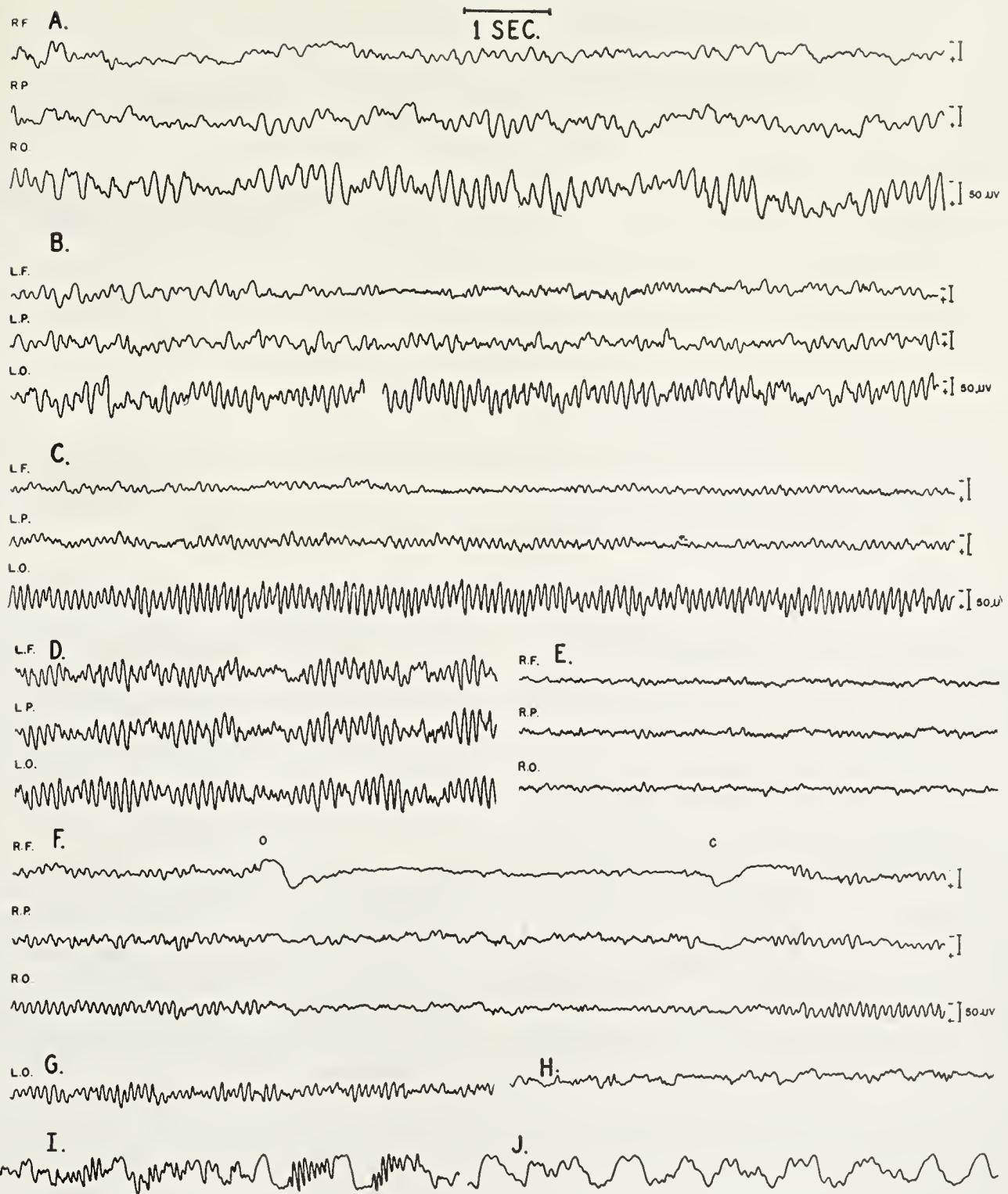


FIG. 88. Normal electroencephalographic patterns.

(A) One-year-old male. EEG: High-voltage 6 to 7 per second waves in occipital lead, less and lower voltage in parietal lead, and still less in frontal lead.

(B) Six-year-old male. EEG: Almost continuous 10 per second activity in occipital lead, 9 and 10 per second in parietal lead, and scattered 6 per second waves in frontal lead.

(C) Fourteen-year-old male. EEG: Continuous 11 per second activity in occipital lead. Parietal lead differs from occipital lead by lower voltage and many 22 to 24 per second (beta) waves. Frontal lead like parietal lead but shows lower voltage.

(D) Twenty-two-year-old male. EEG: High alpha type pattern.

(E) Twenty-one-year-old male. EEG: Low-voltage fast type of pattern.

(F) Twenty-nine-year-old male. Effect of pattern vision upon EEG. At o eyes were opened. Note disappearance of alpha waves and appearance of higher frequencies. At c eyes were closed. Normal pattern appears after a short interval.

(G-J) Changes in EEG with sleep. (G) Normal waking pattern. (H) Drifting. Note disappearance of alpha waves and presence of 6 to 8 and 18 to 22 per second waves. (I) Moderately deep sleep. High-voltage 4 to 5 per second waves with bursts of 14 to 16 per second waves (sleep spindles). (J) Very deep sleep. Random slow waves.

Symbols: (R) right; (L) left; (O) occipital; (P) parietal; (F) frontal. (Courtesy, Gibbs and Gibbs: "Atlas of Electroencephalography," Cambridge, 1941.)

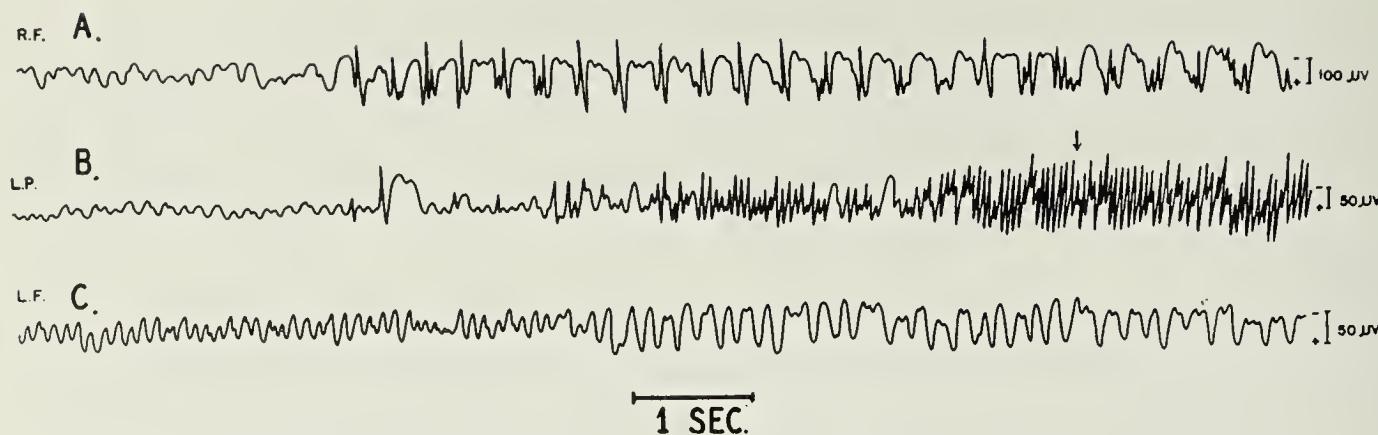


FIG. 89. Three types of abnormal activity.

(A) Thirteen-year-old male. Petit mal: 3 per second spike and wave discharge.

(B) Fifteen-year-old female. Grand mal: high voltage spikes 18 to 22 per second. Arrow marks first visible clinical sign of seizure.

(C) Fourteen-year-old female. Psychomotor discharge. Six per second waves mixed with flat-topped 4 to 5 per second waves. (Courtesy, Gibbs and Gibbs: "Atlas of Electroencephalography," Cambridge, 1941.)

may become accentuated. This procedure is thus frequently used to elicit latent abnormalities.

Anesthetics have a well-defined influence on the EEG, and the action of convulsive and anti-convulsive drugs may be gauged by electroencephalographic observations.

**Abnormal EEG.** The main clinical use of the EEG lies in detecting abnormal rhythms of pathologic origin (cerebral dysrhythmias). These dysrhythmias characterize certain of the epilepsies. They may also arise from pathologic changes induced by cerebral or meningeal scars and tumors, interference with the blood supply, generalized or localized infections, severe hypoglycemia, anoxia, or other causes.

The EEG is therefore often useful in localizing tumors, scars, or areas which may produce

localized abnormal activity not otherwise identifiable by neurologic examinations. It constitutes a definitive method for diagnosing the petit mal group of epilepsies and provides a means of distinguishing between epilepsy and pseudoconvulsions of psychic origin. Figure 89 demonstrates some of the more common abnormal patterns.

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## Section 6—Normal Emotional Development

32

# Personality—Normal Emotional Development

Henry M. Fox

### Scientific Study of Emotional Development

Repression

Emotional Patterns of Infancy

Emotional Patterns of Childhood

Emotional Patterns of Adolescence

Emotional Patterns of Senescence

Role of the Physician

### Scientific Study of Emotional Development.

Scientific observations concerning the profound influence of early emotional experiences on the formation of character and personality constitute some of the most significant recent advances in our understanding of human beings. We have always known, in a general way, that the child is the father of the man, and that "as the twig is bent so grows the tree," but it is only since the work of Freud that it has been possible to discover the specific way in which early personal relationships provide the foundation of character.

The information has been obtained from a number of sources. The most fruitful of these has been the painstaking observation of what happens during the treatment of patients suffering from the effects of emotional disturbances. In recent years it has been possible to confirm this reconstruction of childhood happenings by direct observation of children themselves.

Information concerning anatomy, physiology, or chemistry can be conveyed to others successfully if the material is well organized and expressed vividly and logically. The situation is very different when dealing with material having to do with human emotions themselves, because the reader inevitably responds in an emotional way to a subject which has so much meaning for each of us. Even to call this fact to his attention may evoke an emotional response arising from the reader's suspicion that he is about to be asked to take something on faith. Actually, however, this is only an attempt to point out that anyone is almost certain to react with a certain amount of feeling to the material being presented, and that he is apt to find it difficult to keep his

scientific skepticism entirely free of personal coloration. This is evident to anyone who listens to the intellectual content of a criticism voiced by a student, but who can also be aware of the excited tone of voice in which the comment is made.

Actually, the explanation for this goes considerably beyond the general fact that the subject matter is of such vital importance to every one of us. When it comes to material from childhood, for instance, the reader is not in a position to refer to some of the crucial events in his own life prior to the age of four or five because, without the help of such methods as psychoanalysis, most of us are unable to penetrate the amnesia which veils many of these early experiences from our present efforts to remember them. Perhaps it is because the human being is so utterly helpless for such a long time during his early years that he needs to forget the fears and feelings of guilt which were so overwhelming at a time when he was so poorly equipped to deal with them.

**Repression.** The process of "forgetting" is itself a matter of crucial importance. It is perfectly obvious that we do not remember everything, and this fact has practical advantages as well as disadvantages. Many experiences can be recalled without too much effort, although sometimes we need to be reminded of a past event by other associations. There are other memories, however, which we find it impossible to revive, even with a great deal of assistance. When the physician tries to help a person to recall experiences of this type, he soon realizes that, although his patient may express eagerness to coöperate, there seem to be internal obstacles which defeat his best conscious efforts. These are the emotional experiences which at one time constituted such an overwhelming threat to the young and comparatively weak individual that he was unable to cope with them directly, and could main-

tain a sense of security only by shutting off certain impulses from conscious awareness. This protective "disowning" process begins during the childhood years, and it is a pattern of response rather than a procedure which is consciously decided upon. The dangerous impulses are usually aggressive or sexual in nature, and they are characterized by the primitive intensity of childhood. Repressed memories are of particular significance for understanding human behavior, because they remain intact and unmodified by the subsequent experience of the individual, because the emotional energy continues to exert pressure for some kind of motor expression, and because the individual builds up a highly elaborate system of defenses in order to prevent the eruption of these impulses into conscious activity. Clinical symptoms, such as weakness and apathy, may represent the end result of the diversion of energies from the demands of everyday reality, in order to keep these defenses intact. Dreams and phantasies may represent the only way in which forbidden impulses can be expressed with safety, and even here their true meaning is more or less heavily disguised. It is because the autonomic nervous system and various humoral pathways are subject to pressure from impulses which have been repressed, that we need to pay so much attention to these forces as part of our study of human physiology.

The whole matter of repression is apt to be regarded as rather unreal and abstract, unless we make some effort to imagine what the world is like to a small child who not only must deal with the adult giants who are so much more powerful than he, but also must cope with the intense, unorganized impulses which threaten to overwhelm him from within. Survival, in an entirely literal sense, depends on the degree to which the adults are willing to protect him. It is important to remember, in this regard, that the clear differentiation of the self from the outside world is a comparatively late achievement. The child has to go through a great deal of experimentation before he is able to delineate the borders of his body and his personal influence from the surrounding forces of the universe which all seem within reach of his hand and mouth. Both the infant and the primitive person reluctantly give up their conceptions of a world which is merely the projection of their own strongest feelings. When a child is overwhelmed by an aggressive impulse, he may have some difficulty in clearly distin-

guishing whether the source of hostility is within himself or whether it is coming from those around him. In other words, even a child's hostile wish is felt to be punishable by angry retaliation from the person who is the object of the child's aggression. In this connection it is well to remember that children share the belief of primitive people that the wish is magically equivalent to the deed.

**Emotional Patterns of Infancy.** The child's relationship to the outside world is largely somatic, and abstract language develops long after some of his most crucial personal relationships have been established. His earliest personal feelings are naturally focused on the person who feeds him, and it is while he is sucking in milk that he is also learning about his mother's love for him. Thus, from the very beginning, the gastrointestinal tract becomes significant in terms of personal relationship as well as for the ingestion of food. Many of the early feeding disturbances, for example, can be understood only as the expression of a kind of physiologic language. The baby's refusal of food, for instance, may indicate a negative response to the mother's attitude long before the child has the ability to express his feelings in words. The child's early experience of passive dependence on his mother thus becomes inextricably associated with the process of filling the mouth and stomach with food. It is to be expected, therefore, that later disturbances of the emotional life which involve repressed feelings connected with the need to be dependent are very apt to be expressed according to the original somatic pattern.

In his epoch-making "Three Contributions to the Theory of Sex," Sigmund Freud drew attention to certain specific phases in the process of emotional maturation. He pointed out that there is a close relationship between the instinctual gratification derived from certain mucoslined openings of the body (particularly the mouth, the anus, and the urethra) and the way in which the growing child learns to express his strongest feelings long prior to the development of verbal language. The thumb sucking of infancy illustrates the use of the mouth as a source of sensual gratification, in addition to its function of taking in food. With the development of teeth the infant develops a capacity for a more active incorporation of whatever seems interesting, including not only food but other objects as well. Possession at this stage of development is all too

apt to be equivalent to destruction. Among primitive tribes there is a tendency to devour the object of admiration, and there is an associated magical belief that by eating the heart of a lion, for instance, it is possible to become the possessor of the lion's strength. The powerful instinctual urges expressed in this way explain some of the later personality conflicts arising from an unconscious need for passive gratification, along with biting hostility and gnawing feelings of envy. The presenting symptoms may be primarily disturbances of oral activities such as alcoholism, obesity, anorexia nervosa, certain forms of vomiting, or duodenal ulcer.

The other end of the gastrointestinal tract becomes a special focus of interest a little later in the development of the infant. The instinctual satisfactions connected with the production and retention of feces reach their height just about the time when the grown-up environment begins to make demands concerning the regulation of these functions. When the child feels that too much is being required of him without sufficient rewards in the form of approval and affection, he is apt to express his negative feelings in terms of what one might describe as sphincter language. The pleasure in withholding the fecal mass may become transformed into character traits such as stubbornness, stinginess, or excessive orderliness. Reactivation of these conflicts in later life may result in certain types of constipation. Or the negative feelings may be expressed as a hostile explosiveness which may become the anlage for certain forms of diarrhea and colitis.

**Emotional Patterns of Childhood.** When the child gets to the ages of three, four, and five, he has acquired a more full-fledged sense of his own individuality and is also able to differentiate the people around him. The father, whose role up to this time has been described as that of a kind of assistant mother, now takes on an entirely different significance, and the child finds himself for the first time in what might be described as the primary triangle situation. The boy becomes aware of a specific and active interest in his mother, who is different from his father. At the same time that he is developing the urge for exclusive possession, he makes the discovery that his powerful father has rights in regard to his mother from which he himself is excluded. By imitation of his father he hopes to obtain the strength which he fears but also admires. Again, these vital human relationships and attitudes are

symbolized in somatic rather than in verbal terms. The little boy becomes very much aware of the fact that it is his genitalia which differentiate him from the opposite sex. His discovery of the pleasurable sensations obtainable from stimulation of this area undoubtedly helps to emphasize its importance. When the progress of emotional development is blocked for one reason or another, there may be a regression to the earlier oral, anal, or urethral interests. If the little boy has been unable to free himself from his dependence on his mother, for instance, or has had to cope with a father toward whom he felt so much hate or contempt that he was unable to carry out the normal process of identification, he is apt to feel that his masculinity is severely threatened. It has become so dangerous for him to compete in any way with his father that there is a tendency to turn to his mother for protection, and even to assume a kind of feminine protective coloration, with serious consequences for his own masculine growth and development. The failure to progress beyond the pregenital conflicts helps to explain the origin of the adult oral and anal sexual perversions, as well as certain aspects of homosexuality. The specific disturbances of genital function encountered in the adult, such as frigidity in women or impotence in men, are always related to conflicts in the emotional life having to do with the way in which the original triangle situation was solved. The unsolved attachment to the mother may be unconsciously transferred to the wife, and the rivalries with the father may show themselves as illogical terror, experienced in situations such as school examinations, where the person may feel that some powerful masculine authority will destroy his capacity to achieve full-fledged masculine membership in the tribe. In the little girl, the discovery of sexual differences often leads to a painful sense of inferiority which becomes very much intensified in a family situation where masculine privileges are overemphasized. The little girl, who has just as fierce an interest in the ownership of her body as her brother, tends to believe that she has somehow been deprived of an appendage which rightfully belonged to her. Phantasies regarding menstruation, defloration, and parturition tend to reinforce the primitive conviction that she has been genetically wounded. When the girl is able to identify herself with her mother, it is easier for her to accept the fact that, although she does not have a penis, she does have

the power to give birth to a baby. Such considerations explain some of the disturbances in the menstrual function during maturity and at the menopause. They also account for certain physiologic and emotional problems arising in connection with pregnancy and parturition.

As has been indicated above, the process of identification with the parent of the same sex is of great significance in the establishment of a secure adjustment to masculinity or femininity. This identification is more than a partial aping of certain external mannerisms. The child takes over in a very complete way the basic attitudes of the parental model. This capacity for a rather permanent internalization of the parental influences makes it possible for the young individual to grow up with security, and also to build within himself a capacity for control and self-regulation. In the child's need to manage his turbulent instincts he internalizes the regulative attitudes of his parents, and this becomes the pattern of his conscience which is thus directly inherited from the parental model. The strength and energy of the conscience is derived from the instinctual forces which the individual must master. If the original relationship to the parents has been largely affectionate and friendly, the conscience will function throughout life in a manner which is not felt to be excessively alien and tyrannical.

**Emotional Patterns of Adolescence.** All of these childhood patterns reach a new peak of significance at adolescence. The chief physiologic events are the development of the secondary sex characteristics and the marked acceleration in growth. The chief psychologic problems arise from the increased strength of the sexual instincts and the process of emancipation from the family. It is of great significance for the individual that it is just at the time when he is learning to dispense with parental control that his instincts have become most difficult to manage. This may lead to a temporary intensification of the forces of the conscience, and in some instances there may be an exaggeration of asceticism and a kind of pseudointellectuality which represent the individual's anxious attempts to keep his instinctual life in check.

**Emotional Patterns of Senescence.** In this discussion so much emphasis has been placed on childhood and adolescence because these patterns are unconsciously repeated in new situations throughout the mature life of the individual, and it is evident that character and personality at-

tain a relative stability as the person grows up. It has even been suggested that senescence repeats adolescence in reverse, and the psychology of women at the time of the menopause or of men at the time of vocational retirement certainly tends to bear this out. The woman who has invested her mature energies in the rearing of her children, for instance, now finds that she has time to spare. If during childhood and adolescence she has depended too much on her physical beauty as the sole source of personal security, the cessation of the ovarian function and fears of physical fading are apt to bring a new intensification of old anxieties which hitherto have been successfully submerged. If she has never been able to emancipate herself from her relationship to her parents and has tried to bind her children to herself in the same way that she was bound to her own parents, the process of aging may be a cruel and painful experience. The man who has never been able to come to any very satisfactory terms with his original rivalries in the triangle situation, and who may have transferred these rivalries to his brothers, is sure to have more than the usual difficulties later in life with his associates, whose promotions and preferments he envies. When he reaches the age of retirement, he is apt to resent the younger men who replace him in the vocational situation and with whom he can no longer compete successfully in the sexual sphere.

**Role of the Physician.** It is because of the fact that patients unconsciously react to the physician himself as a substitute parental figure, that it is possible for him to be especially helpful to them. It has been shown that with time and skill much can be accomplished to bring about a more satisfactory solution of childhood problems which have unconsciously persisted into the years of adult life, and thus to correct some of the basic disturbances of good health.

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## Part III

# REACTIONS TO STRESS AND TO ANTIGENIC SUBSTANCES

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## Section 1—Reactions to Injury and Stress

Understanding of the effects of injury on the human organism has, naturally, come more slowly than recognition of the manifestations of injury. At first the febrile response, then leukocytic changes, and, within the past three decades, alterations in the sedimentation rate of the erythrocytes have been utilized as indices of injury and the body's reaction to it. These, however, are but the more obvious signs of a phenomenon, the reaction to injury, which involves the organism as a whole and entails the participation at least of the pituitary and the adrenal glands, the liver,

the kidneys, and the hemopoietic tissues, and results in alterations in circulation and in protein, carbohydrate, and fat metabolism as well as in various electrolytes. In addition, the psychologic reaction to stress is obviously extremely important and therefore deserves special consideration.

It is the purpose of the present section to describe some of these reactions and to attempt where possible a correlation between the clinical observations and present knowledge of the physiologic processes concerned.

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## Reaction to Injury

Paul B. Beeson, M. M. Wintrrobe, and B. V. Jager

### Fever

Control of Body Temperature  
Normal Body Temperature  
Pathogenesis of Fever  
Subjective Symptoms of Fever  
Classification of Febrile Diseases  
Problem of "Fever of Undetermined Etiology"  
Diagnostic Procedure in "Fever of Undetermined Etiology"

Changes in Circulating Leukocytes  
Alterations in Erythrocyte Sedimentation Rate  
The "Alarm Reaction"  
Alterations in Protein Metabolism  
Changes in Total Protein  
Changes in Plasma Fibrinogen  
Changes in Serum Albumin  
Changes in Total Serum Globulin and in Globulin Fractions  
Alterations in Carbohydrate and Fat Metabolism  
Changes in Electrolytes  
Anemia  
Renal Damage

### FEVER

#### CONTROL OF BODY TEMPERATURE

The mechanisms for control of body temperature are so efficient that a healthy person can engage in widely different activities or subject himself to the most diverse conditions of environment with only slight variation in his temperature. By contrast, a sick person lying quietly in bed may show considerable fluctuation, as if the "thermostat" had lost its sensitivity; or his temperature may be maintained at a higher than normal level, as if the adjustment of the "thermostat" had

been altered. Elevation of the body temperature is, in fact, such a sensitive and reliable indication of the presence of disease that thermometry has become one of our commonest clinical procedures.

Much study has been devoted to the subject of body temperature regulation. The ways in which heat can be produced and dissipated have been elucidated, and the cerebral centers for control of body temperature have been accurately located. On the other hand, little is known about the relative importance of various kinds of stimuli to which the cerebral centers react, or about the pathogenesis of fever. In the pages to follow, after reviewing some of the established facts, certain theories of the pathogenesis of fever will be considered, and various classes of febrile illness will be discussed.

The principal source of body heat is the combustion of foods. Although this occurs everywhere in the body, the greatest amount of heat is generated in two places: the liver and the voluntary muscles. Heat production in the voluntary muscles is of particular importance in temperature regulation, because the quantity can be varied according to the need. In most circumstances this variation consists of small increases and decreases in the number of nerve impulses to the muscles, causing inapparent tensing or relax-

ing. When, however, there is a strong stimulus for heat production, muscle activity may increase to the point of shivering, or even to a generalized rigor.

Heat is lost from the body in several ways. Small amounts are used in warming of food or drink, and in the evaporation of moisture from the respiratory tract. The principal heat loss takes place on the surface of the body, where radiation, convection, and evaporation all play a part. The relative importance of these processes depends upon environmental factors. When the surrounding air is cool, radiation and convection are the principal channels, but in a warm environment they become ineffectual. When the outside temperature is equal to or above that of the body, the only possible means of heat loss is evaporation of water.

The principal method of regulating heat loss is by varying the volume of blood flowing to the surface of the body. A rich circulation in the skin and subcutaneous tissues serves to carry heat from deeper portions of the body to the surface, where it can escape. In addition, sweating increases heat loss by providing water to be vaporized; this is under control of cholinergic elements of the autonomic nervous system. When the need is for conservation of warmth, adrenergic autonomic stimuli cause a sharp reduction in the blood flow to the surface. This transforms the skin and subcutaneous tissue into layers of insulation.

The control of body temperature, integrating the various physical and chemical processes for heat production or loss, is a function of cerebral centers located in the hypothalamus. An animal whose brain stem has been sectioned below the hypothalamus loses ability to control body temperature, which consequently tends to vary with the environment. Section of the brain stem above the hypothalamus leaves temperature regulation intact. The exact position of the thermoregulatory centers in monkeys and cats was worked out by Ranson and his associates. They found that stimulation of areas in the anterior portion of the hypothalamus caused activation of mechanisms for heat loss, such as sweating and panting. Stimulation of the caudal part of the hypothalamus activated mechanisms for warming the body and conservation of heat, such as shivering and erection of hair. Clinical experience indicates that the thermoregulatory centers have similar

locations in human beings. Lesions which damage the anterior portion of the hypothalamus may be associated with high levels of body temperature, while lesions in the posterior part may cause marked hypothermia.

It is probable that the cerebral temperature-regulating centers can be affected by more than one kind of stimulus. Experiments on animals show that variation in the temperature of the blood flowing through the brain can cause activation of the appropriate counteracting mechanisms, either for heat loss or for heat production. There is also experimental evidence indicating that these centers may be stimulated by sensory impulses. That physiologic variations in endocrine function may affect the body temperature is shown by the fact that the mean body temperature of women is higher during the second half of the menstrual cycle than it is between the onset of menstruation and the time of ovulation.

#### NORMAL BODY TEMPERATURE

It is not practical to designate an exact upper level of normal body temperature, since there are small differences between normal persons. There are rare individuals whose temperatures are always elevated slightly above accepted "normal" levels. The physician must use some judgment in deciding what constitutes an abnormal temperature in a given case. In general, however, it is safest to regard an oral temperature above 98.6° F., in a person who has been lying in bed, as an indication of disease, while a temperature above 99.0° F. has the same significance in a person who has been engaged in moderate activity. The temperature may be as low as 96.5° F. in healthy individuals. Rectal temperature is usually 0.5° to 1.0° F. higher than oral temperature.

In all persons the body temperature varies by 0.5° to 2.0° F. during each 24-hour period. The highest temperature is usually attained late in the afternoon, while the lowest occurs during sleep, in the early hours of the morning. The cause of this pattern of variation is not known with certainty. Many writers have attributed the higher level in the late afternoon to the combined effects of digesting food and physical activity. These, together with the temperature-lowering effect of sleep, may be the factors which cause the diurnal rhythm to be established. The rhythm persists, however, sometimes for days or weeks when the time relationships of these factors are

altered, and an exaggeration of the normal diurnal pattern of variation is frequently observed in sick people confined to bed, too ill to eat.

Body temperature may be elevated temporarily to "fever" levels by conditions which overwhelm the mechanisms for heat loss. Examples are hot baths and severe muscular exercise. Children are particularly liable to slight elevations after hard play, since their temperature-regulating mechanisms are not so efficient as those of adults. Elevations such as these hardly deserve the term "fever," which should be reserved for rises in body temperature due to disease.

### PATHOGENESIS OF FEVER

Many different types of disease can cause fever. In some of them the rise of body temperature may be attributable to interference with mechanisms for heat loss or with overproduction of heat. The majority of febrile diseases, however, including such diverse entities as infections, vascular accidents, neoplasms, hemolytic crises, and injuries, have only one factor in common—namely, tissue injury. Several hypotheses have been offered regarding the pathogenesis of such fevers. Some workers have attempted to explain them on the basis of shifts in body water, interfering with the normal mechanisms for heat production and heat loss. This seems inadequate to account for various clinical observations, since many patients with fever display no evidence of disturbance in fluid balance. On the other hand, children with "dehydration" commonly exhibit fever. In the case of adults with extracellular fluid deficit the body temperature is usually elevated when the environmental temperature is high (above 90° F.), and depressed when the environmental temperature is low (below 70° F.).

Recent studies suggest that inflammatory exudates contain a protein fraction capable of causing rise in body temperature. Further investigations of this type are needed.

Most discussions of the pathogenesis of fever conclude, as does this one, with the suggestion that fever is the result of a disturbance in function of the thermoregulatory centers in the brain. This disturbance is produced by tissue injury, either by some product of it or by some alteration in metabolism, but the exact mechanism remains uncertain.

While considering the pathogenesis of fever it

is worth while to note the sequence of events which follows intravenous injection of killed bacteria. The accompanying figure (fig. 90) illustrates a typical temperature response of a human being to intravenous injection of a comparatively

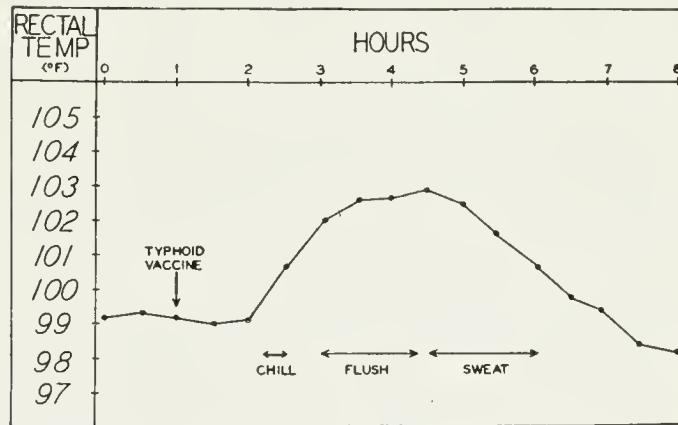


FIG. 90. A typical temperature response of a human being to intravenous injection of a comparatively large dose of typhoid vaccine—100,000,000 organisms.

large dose of typhoid vaccine—100,000,000 organisms. As shown there, the body temperature does not begin to rise until about an hour after the intravenous injection of the pyrogen. Observation of the patient's appearance during this latent period reveals no outward effect; furthermore, he does not complain of any discomfort. Then, rather suddenly, he begins to show signs of malaise; he complains of being cold, and within a few minutes is burrowing down into the bedclothes, asking for more blankets. He begins to shiver, and soon is having a hard, shaking chill which usually lasts 10 to 20 minutes. During this time his skin is pale, cyanotic, and cold to the touch because of intense vasoconstriction. The rectal temperature, nevertheless, is rising steeply. After the subsidence of the rigor the patient gradually begins to feel less cold, and the circulation in his skin increases. By the end of the second hour he is flushed, his skin is hot, and he now complains of feeling feverish. After an hour or so, profuse sweating occurs and the temperature begins to return to normal.

Much remains to be learned about the nature of the series of events which follows intravenous injection of a pyrogenic substance. It has been well established that bacteria are removed from the circulation within a few minutes, by the cells of the reticuloendothelial system. In view of the finding of Ranson, Clark, and Magoun, that cats with hypothalamic lesions gave bizarre tempera-

ture responses to pyrogen injections, it can also be taken for granted that the febrile reaction to a bacterial vaccine involves some effect on the thermoregulatory centers in the hypothalamus. How does the injected pyrogen affect these centers? Considering the latent period which intervenes, there is little likelihood that the pyrogen has a direct effect on them. It seems more probable that the fever is secondary to injury, since the pyrogenic fractions of bacteria are known to be capable of producing widespread capillary damage. The hypothalamic centers could be affected by this injury through afferent nerve pathways, through some alteration in metabolism, or through the agency of some substance discharged into the blood stream from the site of injury.

#### SUBJECTIVE SYMPTOMS OF FEVER

The perception of temperature elevation by patients varies enormously. There are individuals who can tell with considerable accuracy whether their body temperatures are elevated. This perception seems to depend principally upon a sensation of warmth in the skin. Other persons have no subjective symptoms of fever, even in the presence of considerable temperature elevation. For example, patients with tuberculosis may be wholly unconscious of body temperature elevations as high as 103° F. As pointed out in the preceding section, during a period of rapid temperature elevation a patient may actually feel cold. Often, also, patients are not conscious of fever because of the presence of other more unpleasant symptoms such as headache and pleuritic pain. The pain usually experienced in muscles and in the back during acute febrile diseases seems to be due to an effect of the infectious agent, and not a direct manifestation of fever.

#### CLASSIFICATION OF FEBRILE DISEASES

##### Diseases Affecting Thermoregulatory Centers.

As has already been mentioned, disease of the regulatory centers in the hypothalamus may affect body temperature. Cases have been observed in which there was destruction of the centers controlling heat-conserving mechanisms, with resulting hypothermia. More commonly, cerebral lesions are manifested by higher than normal body temperature; this may occur with tumors, infections, degenerative diseases, or vascular accidents. It is not uncommon in cerebral vascu-

lar accidents for the temperature to rise to 105° to 107° F., during the last few hours before death of the patient.

##### Diseases in Which There Is Increased Heat Production.

Patients with thyrotoxicosis frequently have an elevation in temperature—1° to 2° F. above the normal range. This is usually ascribed to the increased amount of heat produced by an increase in the activity and rate of the metabolic processes. Dinitrophenol, a drug which was formerly used for weight reduction in obese persons, causes elevation of temperature; this, too, seems to be caused by an increased metabolic activity, produced by some mechanism outside the thyroid.

##### Diseases in Which There Is Impairment of Heat Loss.

Heat stroke is an interesting example of fever due to interference with the controlling mechanism. Here the mechanisms for cooling the body suddenly seem to fail and the patient ceases to sweat, despite the fact that his temperature is rising. Some of the highest temperatures ever observed in human beings (112° to 113° F.) have been in cases of heat stroke. A temperature higher than 114° F. is not compatible with life.

Patients with congestive heart failure nearly always have an elevation of body temperature. Usually this is only a matter of 0.5° to 1.5° F. It has been thought by many that the elevation is caused by impairment of heat dissipation as a result of diminished cardiac output, decline in cutaneous blood flow, and insulating effect of edema. Others have objected to this idea because patients with congestive heart failure are likely to have other causes of fever, such as venous thrombosis, embolism, myocardial infarction, rheumatic fever, and urinary tract infection. However, since slight fever is so regularly present, even in the absence of such complications, it would appear that the circulatory disturbance may be responsible.

Patients with extensive skin diseases such as ichthyosis, or with congenital absence of sweat glands, may have fever in a warm environment because of inability to lose heat from the surface of the body.

One puzzling cause of fever which may belong in this category is gastrointestinal hemorrhage. A patient who suffers a large hemorrhage into the upper part of the gastrointestinal tract is likely to have fever for a day or two. This cannot be ascribed solely to the introduction of a large

amount of blood into the intestinal tract, because it has been shown that the administration of blood to normal persons through a stomach tube does not cause fever. It is conceivable, however, that in the presence of diminished cutaneous blood flow as the result of blood loss, the heat produced by digestion of a large amount of protein could produce an elevation of the body temperature.

**Diseases in Which There Is Tissue Injury.** Due to the inadequacy of our knowledge about the pathogenesis of fever, most febrile diseases must be classified in this group: (1) It is safe to generalize that all *infections*, whether caused by bacteria, rickettsia, viruses, or more complex parasites, may cause fever. In spite of this fact, however, there is too often a tendency to assume that infection is the only important cause of fever. (2) *Mechanical injury* frequently gives rise to temperature elevation. The duration of this kind of fever is rarely more than one or two days. (3) The majority of *neoplastic* diseases can cause fever. Carcinoma of the stomach or pancreas, with metastasis to the liver, is nearly always associated with temperature elevation. Hypernephroma can produce a hectic type of fever with daily chills. The lymphomatous group of diseases deserves special mention. Lymphosarcoma, leukemia, and Hodgkin's disease may have fever as a prominent early manifestation. (4) A *hemolytic crisis*, as in sickle-cell anemia or in a drug sensitivity reaction, may cause considerable temperature elevation. (5) *Vascular accidents* of any magnitude nearly always cause fever. Examples are myocardial infarction, cerebral hemorrhage or thrombosis, and peripheral vascular occlusion. The temperature elevation in these conditions is probably related to tissue injury in the area where the blood supply has been impaired. (6) *Diseases due to immune mechanisms*, or *inflammatory diseases of uncertain etiology*, constitute an interesting group of febrile diseases. These include drug fevers, rheumatic fever, periarthritis nodosa, disseminated lupus erythematosus, dermatomyositis, and temporal arteritis.

#### PROBLEM OF "FEVER OF UNDETERMINED ETIOLOGY"

The diagnosis in patients with fever of undetermined etiology is a matter of great interest in the practice of internal medicine. The problem is less common now than before the advent of the

sulfonamides and penicillin, since many pyogenic infections are eradicated by these agents without their exact location being known. It is rare nowadays to encounter an individual with fever of any duration who has not already received a trial of therapy with these agents.

Cases of fever of undetermined etiology can be divided into two general groups, according to the duration of the fever. Those of short duration—one to three weeks—are in most instances acute infectious diseases due to agents that are either difficult to recognize, or are not yet identified. Many of them are probably viral infections. In the absence of distinctive signs such as rash or unusual blood picture, the diagnosis cannot be made clinically. Failure to make a diagnosis in these cases is simply a reflection of the inadequacies in our knowledge of acute infectious diseases.

More puzzling are the fevers of undetermined etiology which persist for considerable periods of time. In this group of cases diagnosis is frequently achieved after prolonged observation, although in some instances unexplained fever may persist for months or years:

**1. Chronic Infections.** *Tuberculosis* in some location other than the lungs may cause fever for a long time, without any localizing symptom. Certain *mycotic infections*, such as actinomycosis and blastomycosis, may behave similarly. *Brucellosis* is capable of causing a prolonged fever, but this diagnosis should be made with caution. There is no more justification for ascribing a given fever to brucellosis because of a positive skin test than there is for making a diagnosis of active tuberculosis on the basis of a positive tuberculin test. The only certain criterion for the diagnosis of brucellosis is positive culture, although a high or changing agglutination titer is strong presumptive evidence in favor of this diagnosis. *Malaria* must always be thought of and searched for. *Tertiary syphilis*, especially gumma of the liver or bone, may cause prolonged fever. *Chronic meningococcemia* should be considered, and repeated blood cultures—as many as 15 or 20—may be necessary to prove the diagnosis. *Subacute bacterial endocarditis* should be thought of in any patient who has fever and a heart murmur.

**2. Asymptomatic areas of pyogenic infection** need to be searched for. As mentioned previously, these do not cause as much difficulty now as formerly, because of the common practice of giving

trial courses of effective chemotherapy. Certain foci of sepsis may, however, persist in spite of chemotherapy. Particularly careful search should be made for infection in the paranasal sinuses or in the region of the deep vessels of the neck, in the liver, in the perinephric or subdiaphragmatic regions, the urinary and biliary tracts, and the spinal epidural space.

**3. Neoplasms.** The *lymphomatous group of diseases*, including the *leukemias*, are of special importance as causes of unexplained fever. *Hodgkin's disease* located principally in the abdominal lymph nodes may produce a baffling clinical picture. The same may be said of *carcinoma of the stomach, pancreas, or kidney*.

**4. The Inflammatory Diseases of Uncertain Etiology.** *Periarteritis nodosa*, *lupus erythematosus*, *dermatomyositis*, and *rheumatic fever* may at all times have fever as their outstanding manifestation. A correct diagnosis would depend on the clinical picture and appropriate laboratory tests, including biopsy. The importance of *regional enteritis* as a cause of obscure fever in patients presenting a story of mild diarrhea, and sometimes having arthritis and conjunctivitis, has recently been emphasized. In such instances the cause of the fever remains undiscovered until the gastrointestinal tract is carefully studied by the x-ray method.

#### DIAGNOSTIC PROCEDURE IN "FEVER OF UNDETERMINED ETIOLOGY"

The diseases just listed are the ones most likely to cause diagnostic difficulty among febrile illnesses. When confronted with such a problem, the physician's chances of early correct diagnosis will depend to a considerable degree upon his familiarity with the various manifestations of these diseases. Considering their diversity, it is obvious that no set line of investigation can be followed in studying such cases.

The history and physical examination are of the greatest importance. Knowledge that the patient visited a certain geographic locality, that he drank unpasteurized milk, or that he went hunting and skinned a rabbit, may be the clues which lead to the identification of specific infections. A careful history by systems may elicit a symptom which was not volunteered by the patient, and thus point the way to discovery of an area of sepsis or neoplasm. Thorough physi-

cal examinations should be made at repeated intervals, and findings such as petechial spots or enlargement of the spleen, liver, or lymph nodes, which develop during the course of the illness, are likely to prove especially valuable clues.

Laboratory studies include, of course, examinations of the blood, urine, and feces; x-ray of the chest and gastrointestinal and urinary tracts; agglutination tests; and serologic tests for syphilis. Agglutination tests should be repeated at weekly intervals during the first part of a febrile illness. Antibodies cannot be expected to be present before the end of the first week, and they frequently do not appear until two or even three weeks. A changing titer is usually more significant than a single high titer. Skin tests should also be repeated from time to time. The appearance of a positive tuberculin test during the course of an illness, or change from a positive to a negative tuberculin reaction would be strong evidence of active tuberculosis. If skin tests for brucellosis are employed it must be remembered that these may stimulate a rise in titer of agglutinins for *Brucella* organisms.

Certain points should be kept in mind in connection with blood culture. This test should be made repeatedly. Bacteria seldom live and grow in the circulating blood; indeed, it seems unlikely that they remain in the blood stream for more than a few seconds or minutes before being removed by the reticuloendothelial cells. Unless an infection happens to be one which constantly feeds organisms into the blood stream, the obtaining of a positive blood culture is a matter of chance. It is worth while, therefore, to take at least three to six cultures a day for several days. There is no advantage in waiting until the temperature is high, since, as was shown in the discussion of the chill reaction to typhoid vaccine, fever does not reach its maximum until some hours after invasion of the blood stream. Arterial cultures offer no advantage over culture of venous blood, as few organisms are removed from the circulation by the superficial tissue of the hands. Culture of the sternal marrow is occasionally positive when the peripheral blood yields no growth, especially in *Brucella*, typhoid, and other *Salmonella* infections. Animal inoculation may be necessary for the demonstration of certain infections such as tuberculosis, toxoplasmosis, and many viral diseases.

If examinations yield no evidence of infection,

and especially if the patient is past middle age, the presence of neoplastic disease deserves special consideration. Endoscopic and special x-ray examinations are in order. Repetitions of the physical examination may eventually disclose an abnormal finding. Superficial lesions in the skin and lymph nodes should be subjected to biopsy. Biopsy of tissue from deeper areas such as liver may also be helpful.

In the event that careful examinations fail to give the diagnosis, therapeutic trials are justified. These include the use of such agents as the sulfonamides, antibiotics, emetine, antimalarial drugs, and radiation.

### CHANGES IN CIRCULATING LEUKOCYTES

In the adult the leukocytes normally are maintained at a rather steady level between 5000 and 10,000 cells per cu. mm., with an average of 7000. During infancy the leukocyte count may be very irregular, and until 26 weeks of life variations from 5000 to 24,000 may occur in the absence of demonstrable disease. In childhood the range of variation tends to decrease, and the general average becomes lower as adult age is approached. The leukocyte count is affected by many factors, including even the state of physical and mental rest. Fluctuations in the leukocyte count occur during a single day, as well as from day to day. Strenuous exercise can produce a marked leukocytosis, and the act of labor, paroxysmal tachycardia, and convulsive seizures may do the same. Pain without associated infection or major tissue damage has been observed to cause leukocytosis, and so also have nausea and vomiting. These changes are probably not due to new formation of cells but are caused by mobilization of leukocytes from the lungs, liver, spleen, and other organs, where they lie in close proximity to the small blood vessels. Such a leukocytosis can be distinguished from the leukocytosis associated with tissue injury, especially that seen in infection, by the increase of young cells which accompanies the latter.

As measures of the reaction of the body to noxious agents, alterations in the total number of leukocytes and in their relative proportions are of considerable significance. In many instances, the alterations in the total and relative numbers of the leukocytes are of such a character that the nature of the noxious agent may be suspected.

The changes which may occur may involve all three types of leukocytes—namely, granulocytes, lymphocytes, and monocytes. It is to be emphasized that this discussion considers fluctuations in total numbers of these cell components rather than percentile fluctuations.

The most common change, an *increase in the number of neutrophilic leukocytes*, is seen in association with acute infections of various types, in intoxications such as those associated with uremia, diabetic acidosis, heat stroke, and injuries such as burns, as well as in poisoning by various chemicals and drugs (digitalis, insect venoms, foreign proteins); in response to acute hemorrhage; postoperatively, perhaps as the result of the extensive tissue injury and liberation of protein; in certain noninfectious conditions such as coronary thrombosis, again perhaps as the result of tissue injury; in association with malignant neoplasms when these are growing rapidly; and following the sudden destruction of red corpuscles.

The magnitude of neutrophilia is influenced by various factors such as: (1) The cause of the neutrophilia. Pyogenic, especially coccal, infections are likely to produce neutrophilia, whereas other infections such as those caused by typhoid or tubercle bacilli do not call forth a neutrophilic response. (2) The localization of the inflammatory process, which tends to cause neutrophilia, even when the organism is one which ordinarily does not produce this change in the leukocytes (thus neutrophilia usually accompanies tuberculous meningitis, but not pulmonary tuberculosis). (3) The virulence of the invading organism, as well as the reactivity of the patient and his general resistance. Thus neutrophilia will be absent when the injury is very mild. It is also lacking, however, when the infection is overwhelming or the patient is too feeble and nonresistant.

Certain infections, instead of producing leukocytosis, cause *leukopenia*. Examples of these include typhoid fever, undulant fever, many infections caused by viruses, and certain protozoan infections (e.g., malaria). Usually, the reduction in cells is due to a marked decrease in the cells of the granulocytic series. Any type of overwhelming infection may be associated with leukopenia, and this change in the blood is frequently observed in association with cachectic and debilitating states or inanition. In anaphylactoid shock and in the early stages of chills, leukopenia

is observed, and this change is also encountered in association with certain conditions of unknown cause such as disseminated lupus erythematosus and in various hemopoietic disorders, especially those involving the spleen, as well as the result of the action of various chemical and physical agents (e.g., radioactive substances) (see p. 766).

Various mechanisms may be concerned in the production of leukopenia. In anaphylactoid shock the neutrophilic leukocytes collect in the internal organs. The leukopenia seen in certain infections has been attributed to the trapping of leukocytes in the alveolar walls of the lungs, in the sinusoids of the liver, and in the spleen. The leukopenia associated with splenic disorders has been attributed to a hormonal effect of the spleen. Destruction of leukocyte-forming tissue, "crowding out" of the bone marrow by abnormal cells, and deficiency of essential nutritive factors such as pteroylglutamic acid, are other possible mechanisms.

Other types of tissue reaction cause *an increase in the number of eosinophilic leukocytes* above the normal. Especially noteworthy in this class are allergic disorders such as bronchial asthma, urticaria, angioneurotic edema, and hay fever, but many skin diseases and parasitic infestations are characterized by such a change in the blood. In addition, certain infections (e.g., scarlet fever) are associated with eosinophilia, as well as various disorders of unknown etiology such as periarthritis nodosa, Loeffler's syndrome, and certain diseases of the hemopoietic system. Following slight or moderate repeated irradiation by roentgen rays, eosinophilia may develop. Curiously enough, during infections in which neutrophilia occurs, the eosinophils are reduced in number or disappear entirely (Simon's "septic factor"). This effect may be mediated through the adrenal glands, since it has been shown that injection of adrenocorticotrophic hormone or adrenal cortical extract can produce a decrease in the eosinophil count.

Still other disorders are characterized by an *increase in the number of lymphocytes*, which may be cells of normal appearance (e.g., pertussis, acute infectious lymphocytosis) or lymphocytes of unusual morphology (e.g., infectious mononucleosis). In certain exanthemas (e.g., mumps, German measles) after the initial stage lymphocytosis appears, and certain chronic infections such as tuberculosis and undulant fever may be

accompanied by this type of change in the blood picture. During the stage of convalescence from an acute infection, lymphocytosis is a common finding. In addition, in various types of tissue injury other than that associated with infection (e.g., moderate exposure to dry heat, sunlight, roentgen rays), lymphocytosis may develop. The lymphocyte seems to be concerned in some way with the body's reaction to foreign protein, and thus is an important element in the reaction to tissue injury. In both man and experimental animals, the administration of adrenocorticotrophic hormone and of certain adrenal cortical steroids produces a decrease in the number of circulating lymphocytes. In certain animal species, these substances also lead to depletion of lymphocytes in certain tissues such as the spleen, lymph nodes, and thymus. Experimental work indicates that, in small animals at least, antibodies are formed or are stored in lymphocytes. One might anticipate that hormone-induced lymphocyte dissolution might lead to an increase in circulating antibodies in animals that have been immunized previously. However, the evidence that this occurs is controversial. It is quite possible that there is considerable species variability in some of the adrenal cortical effects.

An *increase in the number of monocytes* occurs in still other bacterial infections such as tuberculosis, subacute bacterial endocarditis, brucellosis, and typhus. Many protozoal infections are characterized by monocytosis, and so also are certain other diseases such as Hodgkin's disease. *Plasma cells* are rarely found in the circulating blood, but they may be observed in rubella, scarlet fever and other exanthemas, in serum sickness, and even more rarely under other conditions.

These instances have been cited as the most common examples of changes which occur in leukocytes in association with tissue injuries of various types. It is not known whether these hematologic manifestations are the consequence of tissue injury per se or, where infection is the exciting agent, whether they are attributable to the invading organism itself. It would seem more plausible to assume that the observed effect is mediated through the tissue reaction of the host. *The factors which control the leukocytic level* of the blood are not well understood. Thus, for example, it has been generally accepted that leukocytosis depends on *chemotactic attraction* of leukocytes from the bone marrow into the blood stream. A

thorough review of the evidence by McCutcheon has shown that for this supposition there seems actually to be no support. It has likewise been held, by most pathologists, that emigration of leukocytes from blood vessels into tissues is the result of chemotaxis. Both chemotaxis and changes in vascular endothelium probably play a part. Chemotaxis is chiefly important as the reaction by means of which leukocytes are attracted to infecting microorganisms from a distance. It is especially the polymorphonuclear leukocytes that are so attracted. Lymphocytes have not shown chemotaxis to any substance yet tested. There is evidence in tissues that monocytes react chemotactically, but *in vitro* these cells appear to show only weak chemotaxis or none at all.

*Phagocytosis*, it should be noted, is not always preceded by chemotaxis. Thus, for example, monocytes, the most voracious phagocytes, are (in mammals, at least) not definitely known to be attracted to the bacteria and cells that they engulf. Phagocytosis can also take place without the intervention of specific antibodies (opsonins), a phenomenon which requires the support of surfaces of suitable physical properties. Leukocytes have been shown to ingest pneumococci after trapping them against the wall of the pulmonary alveoli. This phenomenon has been called "surface phagocytosis" (Wood).

Microorganisms excite chemotaxis. Bacteria may produce substances in the course of metabolism that attract leukocytes, perhaps by reducing surface tension on the adjacent side. Again, they may injure tissues which then give off attracting substances. The metabolic product which attracts leukocytes is probably a protein or a heat-stable protein derivative. Chemotaxis is also excited by products of injured tissue. Thus large numbers of leukocytes may be found in sterile blebs resulting from burns, as well as in irradiated tissues, and may be attracted by injecting intensely irritating substances such as turpentine. Menkin produced sterile exudates in dogs and obtained by fractionation a thermostable, dialyzable substance having the properties of a polypeptide (leukotaxine). This substance attracted leukocytes both in tissues and *in vitro*. He has been able to separate leukotaxine from a toxic euglobulin liberated by injured cells, necrosin, which causes leukopenia and hastens markedly the rate of coagulation of blood in

*vitro*. According to Menkin, the increase of capillary permeability, and the migration of polymorphonuclear leukocytes associated with inflammation, is primarily referable to leukotaxine, presumably derived from injured cells. This peptide, besides inducing a discharge of immature granulocytes from the bone marrow, also causes a marked hyperplastic reaction of these elements, and of megakaryocytes in the marrow.

### ALTERATIONS IN ERYTHROCYTE SEDIMENTATION RATE

The red corpuscles of normal blood to which an anticoagulant has been added settle down only slowly if the blood is placed in a tube standing vertically. Increased sedimentation rate is an index of tissue injury, inasmuch as it occurs frequently in a variety of acute and chronic diseases, particularly infectious states; but this statement must be qualified, since accelerated erythrocyte sedimentation occurs in a physiologic process such as pregnancy. The rapidity of fall roughly parallels the intensity of the disease process, being greater with greater activity. The finding of an increased sedimentation rate lacks diagnostic specificity, however, other than to indicate the presence of an abnormal state. This test has found special usefulness in serial determinations which afford some indication of the progress of the disease process. Thus it has proved extremely useful in following the course of active rheumatic fever and of pulmonary tuberculosis.

The cardinal factor responsible for increased sedimentation of red corpuscles is the development of clumps of rouleaux which, being of larger volume but having relatively small surface areas, and thus being heavier in relation to the surface area exposed than single red corpuscles, settle out more rapidly. No single factor is known which can account for this tendency to clump. Generally, in acute infection, the increase in sedimentation rate is correlated roughly with the height of the plasma fibrinogen level. To a certain extent, during acute infections, it may be correlated with the height of the alpha-globulin content of the plasma. In certain chronic disease states the increased sedimentation rate seems to be correlated with the increased total globulin. The addition of fibrinogen *in vitro* to whole blood containing an anticoagulant results in a marked acceleration of the erythrocyte sedimentation

rate, while the similar addition of whole globulin produces a definite but less striking increase in the sedimentation rate. In most instances where the sedimentation rate of whole blood is greatly increased, the resuspension of red corpuscles in serum or defibrinated plasma gives very much slower sedimentation rates. It may be that sedimentation rate is not controlled by the absolute concentration of the total plasma proteins, or of the protein fractions, but may depend on the relation of the various fractions to one another.

With marked anemia, even in the absence of demonstrable tissue injury, the sedimentation rate is accelerated. An exception is seen in sickle-cell anemia, perhaps because the peculiar shape of the red corpuscles does not favor rouleaux, and sedimentation is very slow, even when the anemia is very severe. However, since so many factors influence the suspension stability of the red corpuscles, the use of various charts to correct the influence of anemia may give misleading results. In instances of polycythemia the sedimentation rate is greatly retarded, and may be found to be normal even in the presence of severe infections. Other factors influence the sedimentation rate, but are poorly understood.

It should be emphasized that an increase in sedimentation rate is a nonspecific reaction. As already stated, a physiologic increase occurs during pregnancy. In general, sedimentation rate is increased in most acute systemic infections, while in localized acute inflammatory conditions variations in sedimentation rate depend on the nature and severity of the morbid process. Thus, in acute nonsuppurative inflammation, such as influenza, the rate tends to be normal, whereas in localized acute suppuration, such as pelvic inflammatory disease, there may be a pronounced acceleration even when the pulse and temperature are normal. For example, the sedimentation rate is often normal early in acute appendicitis but is greatly accelerated in the presence of pelvic inflammatory disease. Again, in chronic localized infections, the rate varies with the extent and nature of the infection. Uncomplicated new growths are not necessarily associated with rapid erythrocyte sedimentation, even when malignant. In the case of malignant tumors, sedimentation tends to be accelerated when the tumor is very vascular, when there is a tendency to break down, and when there is much reaction about the tumor.

Accordingly, elevations of the sedimentation rate may be found in such varied conditions as pregnancy, acute and chronic infection, and in the presence of malignancy. In addition, increases may occur in serum sickness, in a large group of diseases of unknown etiology such as rheumatoid arthritis, rheumatic fever, glomerulonephritis, disseminated lupus erythematosus, and many other conditions. Elevation of the sedimentation rate occurs in various forms of liver disease which are not infectious in character, and even during acute attacks of gout. It must be added that not all infectious states are associated with an elevation of the sedimentation rate. A significant increase rarely occurs in acute anterior poliomyelitis. A normal erythrocyte sedimentation rate has been observed in as many as 20 to 30 per cent of instances of active pulmonary tuberculosis. Again, in acute rheumatic fever, the sedimentation rate, initially greatly elevated, may fall to normal with the advent of congestive heart failure, even though obvious rheumatic activity persists. It may be added that congestive heart failure from any cause tends to abolish the conditions which favor rapid sedimentation of the red corpuscles.

As already indicated, fever, changes in leukocytes, and an increase in erythrocyte sedimentation rate are but the more obvious and readily measurable evidences of a phenomenon which involves the organism as a whole:

#### THE "ALARM REACTION"

This descriptive title has been applied by Selye to a series of events which may be elicited by any type of stress to which the organism is exposed. Such varied stresses as emotional disturbances, hemorrhage, trauma, exposure to cold, fever, injection of epinephrine, or almost any other change in the internal or external situation which might be considered as putting "stress" on the organism will elicit the entire reaction. Its intensity is in some measure proportional to the severity and duration of the stress.

The alarm reaction is mediated through the secretion of adrenocorticotrophic hormone (ACTH) by the pituitary, which in turn stimulates the adrenal cortex to elaborate and discharge its steroid hormone (or hormones). By the use of highly purified ACTH and synthetic and natural adrenal steroids it has been possible to demonstrate that many of the reactions to injury are

mediated by this mechanism. The effects are conveniently discussed in terms of the effects on protein, fat, and carbohydrate metabolism, on electrolytes, and on lymphoid tissue and the circulating blood cells. Reference has been made already to some of these changes. The 11,17-oxycorticosteroids cause lysis of lymphoid tissue and of circulating lymphocytes. The effect on eosinophils is even more striking. When eosinophil counts are made by a direct technic, they number 200 to 400 per cu. mm. under normal conditions. Under conditions of stress, their number is reduced to very low levels (0 to 50 per cu. mm.) if the adrenal cortex is normal. The same steroids cause an increase of the other granulocytic cells, particularly the polymorphonuclear neutrophils, and the over-all effect on the leukocyte count usually is a leukocytosis. It will be noted that the total reaction with leukocytosis, increased neutrophils, and decreased lymphocytes and eosinophils, is like that found in many infections. The alterations in protein, carbohydrate, fat, and electrolyte metabolism will be discussed shortly.

Although many of the observed alterations in metabolism during the reaction to injury can now be explained on the basis of the alarm reaction, it seems that other less well-understood processes also play important roles. These probably account for many of the variations found in reactions to different types of injury. That the adrenal alarm reaction is a fundamental part of the reaction of the organism to injury cannot be doubted, however. That it probably is important in protecting the animal from otherwise serious or fatal effects of injuries is apparent if one recalls the greatly altered response of patients with adrenal insufficiency (Addison's disease) and their great susceptibility to trauma and infection.

### ALTERATIONS IN PROTEIN METABOLISM

The normal adult receiving an adequate diet excretes in the urine and stools a total amount of nitrogen which closely approximates the nitrogen intake. This is termed nitrogen equilibrium. When the protein excreted exceeds the intake, there is a negative nitrogen balance. Conversely, under certain conditions, a positive nitrogen balance may occur. Tissue injury, whether by physical trauma, burns, infection, or major sur-

gical procedures, is associated with changes in protein metabolism which may be quite striking. Studies of nitrogen balance show that nitrogen loss occurs, sometimes of marked degree. The extent of this change depends in part upon the severity of the tissue insult. In part, it also depends upon the previous nutritional state of the patient. Thus patients with chronic debilitating disease may show no increased nitrogen loss as a result of superimposed acute trauma. Moreover, patients with chronic illnesses and actively progressing tissue destruction often fail to show a negative nitrogen balance provided the intake can be maintained at a satisfactory level. In the previously healthy individual, the outpouring of nitrogen in response to injury often occurs even when protein is being deliberately furnished in adequate amounts. So difficult is it to interrupt this wasting of nitrogen, even by administering protein hydrolysates or amino acids parenterally, together with increased calories in general, that toxic destruction of protein in association with tissue injury, a "protein catabolic process," has been postulated. Another theory proposes that incoming nitrogen is routed through the liver after trauma, and is wasted before it can be used for anabolism by the tissues, an "antianabolic" effect. A major portion of the negative nitrogen balance appears to be dependent on the release of 11,17-oxysteroids from the adrenal, through the mediation of the pituitary, as the result of tissue injury. The chief effect of these steroids in bringing about the negative nitrogen balance is to produce gluconeogenesis from protein stores. Perhaps in many cases the explanation of the changes observed may be that an increase in the rate of both anabolism (tissue growth) and catabolism occurs in association with injury rather than a change in either process alone, and that the data which have been obtained only reflect the excess of the latter.

Although it has been claimed by some workers that the parenteral administration of a sufficient amount of a mixture of the "essential" amino acids, plus glycine, can produce nitrogen balance or even permit accumulation of nitrogen, it is important to bear in mind that clear evidence of the desirability or the importance of parenteral protein therapy in clinical practice—as, for example, postoperatively—has yet to be furnished. Another matter which must be kept in mind is that the attainment of nitrogen balance does not

mean that individual protein functions may not still be disturbed.

As a result of injury, selective changes in the individual components of the plasma protein may take place which may or may not be reflected in alterations in the total plasma or serum protein. With the newer chemical and physical methods, much additional information concerning the size, shape, amphoteric properties, surface structure, and amino acid content of the various plasma protein constituents has been obtained. In particular, the development of the electrophoretic technic has offered a new quantitative method for protein separation. When plasma proteins are subjected to an electric field under rigidly specified conditions, it is observed that different protein constituents will move with different velocities. By complex optical recording it is possible to determine the mobility of each component, and to estimate quantitatively its concentration relative to the total protein concentration in the electrophoresis cell. On the basis of specific mobilities, it has been found that plasma contains at least five constituents, of which the fastest-moving (in an alkaline pH range) is albumin. Progressively slower mobility characterizes components designated as alpha-globulin, beta-globulin, fibrinogen, and, finally, gamma-globulin. It is recognized that none of these fractions is homogeneous in spite of its distinctive mobility. The albumin, perhaps, is the most uniform. Comparison of electrophoretic measurements with chemical fractionation has led to a critical appraisal of ordinary clinical chemical methods for separation of serum protein into albumin and total globulin, and has indicated that, occasionally, these simple chemical procedures may give rise to grossly misleading results.

Alterations in any plasma protein constituent should reflect an alteration in rate of synthesis, rate of destruction, and external loss of that constituent. Several factors qualify this assumption. Alterations in plasma volume, either physiologic or pathologic, can produce apparent fluctuations in plasma protein constituents as expressed in grams per 100 ml. of plasma, without the total circulating quantity being altered. In addition, a complex and still incompletely understood equilibrium exists between circulating plasma protein, protein present in intercellular spaces, and protein stored in cells, particularly those of the liver.

There is good reason to believe that synthesis of plasma albumin and plasma fibrinogen occurs largely or entirely in the liver. The site of synthesis of the globulins still is an unsettled problem. With the electrophoretic technic, it has been demonstrated that specific antibodies present in human serum are contained largely in the gamma-globulin fraction. That certain antibodies may be formed in the lymphocytes has been pointed out already. The role of both the plasma cells and the reticuloendothelial system in the elaboration of antibodies and circulating globulins remains an unsettled point. As to the synthesis of alpha- or beta-globulins, which in the normal plasma comprise a greater fraction of the total globulin than does the gamma-globulin, very little is known.

As a result of tissue injury, many factors may operate to modify the various protein constituents of the plasma. In hemorrhage or when tissue is traumatized, protein may be lost, externally. With illness, dietary intake of proteins may be restricted. During the acute phases of severe systemic infections and following surgical procedures, as already mentioned, a negative nitrogen balance frequently is found in spite of an adequate or excessive protein intake.

**1. Changes in Total Protein.** The normal total plasma protein, as determined by the Kjeldahl procedure, usually ranges from 6.2 to 8.0 Gm. per 100 ml. Physiologic fluctuations occur which are correlated inversely to a certain degree with alterations in plasma volume. Changes in plasma volume may take place in various disease states to modify the total protein concentration. During acute infections, a significant increase in plasma volume frequently occurs. Likewise, in certain infections dehydration may occur, leading to an apparent increase in the total protein of the plasma or serum. Marked deviations of plasma protein from the normal range are not common, however, during tissue injury. With prolonged illness a decrease in total plasma protein may occur, as exemplified by the changes seen in nonspecific ulcerative colitis and in the nephrotic stage of glomerulonephritis. In certain disorders one encounters a marked hyperproteinemia. In the absence of dehydration this results from a rise in globulin rather than of albumin, which frequently is reduced. Examples include certain cases of cirrhosis, multiple myeloma, kala-azar, schistosomiasis, Boeck's sarcoid,

lymphogranuloma venereum, and occasional cases of rheumatoid arthritis and of chronic infection.

**2. Changes in Plasma Fibrinogen.** In a variety of acute infections, in many chronic infections, in cirrhosis of the liver, and in certain other diseases, an increase in plasma fibrinogen occurs. Not all instances of tissue injury lead to an increase in plasma fibrinogen. The relation of this constituent to the erythrocyte sedimentation rate has been considered already. Significant reduction in fibrinogen rarely occurs, being noted in instances of severe liver damage and in a rare disorder termed congenital hypofibrinogenemia (p. 266). Even more rare is congenital afibrinogenemia.

**3. Changes in Serum Albumin.** Changes in this constituent, as seen in acute tissue injury, especially in the absence of external loss of serum, seem to reflect, primarily, changes in plasma volume. With prolonged disease there usually is a decrease in the serum albumin quite apart from changes in plasma volume. The most severe reductions in serum albumin are seen in the nephrotic stage of glomerulonephritis, where there is an excessive external loss of this substance, and in severe hepatic disease, where synthesis presumably is impaired. Lesser reductions are found in many instances of chronic infection, in instances of impaired absorption of protein such as sprue and other chronic diarrheas, and in open suppurative draining wounds. Rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, periarthritis nodosa (the so-called "diffuse collagen diseases"), all may be accompanied by a significant hypoalbuminemia.

**4. Changes in Total Serum Globulin and in Globulin Fractions.** The total serum globulin, even in "normal" individuals, is subject to considerable fluctuation from day to day. As measured by the Howe sodium sulfate technic, the total globulin in normal persons ranges from 1.2 to 2.5 Gm. per 100 ml. of serum. Instances of marked reduction of serum globulin are infrequent. In the course of acute systemic infections, during the second week, a moderate rise in total globulin frequently occurs and persists for several weeks after subsidence of the infection. Moderate rises in total globulin are found in a variety of chronic disease states. Great increases

in total globulin have been considered already (see p. 412).

The development of the electrophoretic technic has permitted a quantitative estimation of three globulin fractions designated as alpha-, beta-, and gamma-globulins. In certain instances it is possible, on the basis of mobility, to subdivide the fractions even further; for example, alpha-globulin may be separated into alpha<sub>1</sub>- and alpha<sub>2</sub>-globulin.

*Alpha-globulin* shows moderate deviation from the observed range for normal adults in infancy, childhood, and pregnancy. Significant increases in alpha-globulin occur soon after acute tissue injury such as a burn, and in systemic infections. These usually persist only a few weeks. Alpha-globulin may be increased significantly in chronic infections, particularly if active tissue injury is present. Increases occur in certain cases of rheumatoid arthritis and in active progressive tuberculosis. In the latter, this increase has been found to be of prognostic value. Increases also occur in cases of extensive malignant disease. In general, in acute self-limited infections, the rapid early rise in alpha-globulin is similar to that of plasma fibrinogen, as is the rather rapid decline.

*Beta-globulin* seldom deviates significantly from the normal range in tissue injury but may show considerable variation in certain metabolic disorders. Increases in beta-globulin may be observed in some cases of cirrhosis or acute hepatitis, in diabetes mellitus, and in hypothyroidism.

*Gamma-globulin* has aroused considerable interest because of the finding that most specific antibodies in human serums are contained in this fraction. In most acute infections, the gamma-globulin is found to be normal during the first five to seven days. This fraction then increases, often reaching a value twice the initial one during the second or third week of the infection. To a certain degree, this rise coincides with the rise in circulating antibodies. The elevation in an acute infection usually persists for several weeks after subsidence of the disease, but occasionally lasts much longer. Marked increases in gamma-globulin have been observed in many chronic infections such as osteomyelitis, tuberculosis, and subacute bacterial endocarditis. In general, less striking increases have occurred after virus infections than after bacterial infections. Increases in gamma-globulin occur in acute infectious hepatitis, in cirrhosis of the liver, in rheumatoid ar-

thritis, and in the diffuse collagen diseases, as well as in some cases of myeloma and sarcoid. A moderate increase may be encountered in congestive heart failure. Reduction of gamma-globulin is seen in the nephrotic syndrome. Congenital absence of gamma-globulin has been observed.

Although the rise in gamma-globulin appears to be correlated to a certain extent with circulating specific antibody in acute infections, it should be emphasized that, in man at least, the order of magnitude of gamma-globulin increase may be as much as 1000 mg. per 100 ml., whereas the increase in specific antibody rarely would exceed 10 mg. per 100 ml. of serum.

It is thus evident that many factors operate to modify the qualitative composition of the plasma protein. With rare exceptions, the quantitative estimation of the plasma proteins either by chemical or electrophoretic means does not assist greatly in the establishment of a diagnosis other than to demonstrate the presence of an abnormal state which usually is obvious from other procedures. *Indirectly these alterations in protein constituents are measured by such varied laboratory procedures as the erythrocyte sedimentation rate, the cephalin-cholesterol flocculation test, the thymol turbidity test, the gold sol test, the formol-gel reaction, and many other less commonly employed examinations such as the osmotic pressure determination and viscosity measurements. Just as in the case of the erythrocyte sedimentation rate, the serial determination of the protein constituents in a specific instance may offer useful information as to the activity of a disease, the prognosis, and the efficacy of therapy.*

#### ALTERATIONS IN CARBOHYDRATE AND FAT METABOLISM

When the 11,17-oxycorticosteroids are administered in excess, hyperglycemia and glycosuria develop. There is a growing body of evidence that this "diabetes," which is similar to that found in patients with Cushing's syndrome, is not primarily of pancreatic origin but arises in a major degree from other metabolic disturbances. The protein catabolic effect already described leads to excess gluconeogenesis by the liver. It now is apparent that other effects are also important. Studies of the respiratory quotient indicate that the total metabolism is deviated toward the combustion of fat. The demonstration of in-

creased fat mobilization from depots and increased blood ketones under the influence of these hormones suggests that the change in fat metabolism is a primary one. It may also be that peripheral glucose utilization is impaired by interference with some enzyme system—e.g., the hexose-kinase reaction.

#### CHANGES IN ELECTROLYTES

Corresponding with the nitrogen loss already described, there is a loss of sulfur and phosphorus when tissue injury occurs. The total change in serum electrolytes as measured in milliequivalents per liter is usually of small magnitude, but this is attributable in large measure to the fact that changes in plasma and in extracellular and intracellular fluid volume may be great and yet not be reflected in terms of values expressed per unit volume. Excretion of small amounts of sodium and large amounts of potassium is characteristic of many reactions. When the "alarm reaction" is of major proportions, however, a serious electrolyte disturbance may occur. There is a reduction in total electrolytes and severe depletion of serum potassium with an associated metabolic alkalosis, a syndrome which leads to weakness, mental confusion, and many vague symptoms. Administration of potassium seems to reverse much of this metabolic disturbance even in the presence of continued stress. The extensive potassium loss is at least in part the result of the tissue catabolic reaction, a major part of which is mediated via the adrenal cortex. That the electrolyte changes are not solely explainable by implicating the pituitary-adrenal mechanism is indicated by the fact that the administration of ACTH to the human organism causes marked sodium retention, in contrast to the sodium loss frequently seen following tissue injury.

#### ANEMIA

Long-standing infection is associated with the development of anemia. This is also true of full-thickness burns, and even trauma of short duration has been found to be accompanied by a fall in hemoglobin and red corpuscles. In most cases it seems clear that increased blood destruction is not the causative factor. Measurements of total plasma volume suggest that the anemia may be more severe than is indicated by the measurement of hemoglobin per 100 ml. of plasma. In-

vestigation of the pathogenesis of the anemia of infection has shown this to be associated with a disturbance in iron metabolism in which the plasma iron content is greatly reduced below the normal, and iron, even when given parenterally, is not used for hemoglobin synthesis but is carried to sites of iron storage such as the liver. At the same time the quantity of iron-binding protein in the plasma is reduced below normal. The basic mechanism is obscure, and it is not known whether the anemia and the protein catabolic process which accompany tissue injury are related or are entirely independent manifestations of the reaction to injury. In any event, much of the debility associated with tissue injury can be attributed to these two metabolic disturbances. Iron or liver therapy is of no value in the treatment of this type of anemia, transfusions are of but temporary values, and the anemia disappears only when the underlying disorder is successfully relieved.

### RENAL DAMAGE

The crushing of a limb, or occlusion of its arterial supply for several hours, is associated with a train of events which has been called the "crush syndrome." Release from debris or restoration of blood flow is followed by swelling. The limb becomes hard, paralyzed, and anesthetic, wheals appear at the site of compression, and loss of plasma into the area of injury may cause hemoconcentration. Shock may supervene (Chapter 14). Urine passed during the first 24 hours is colored red or brown by myoglobin and its breakdown products, contains albumin, and shows many brown and black pigment casts. Urinary output and specific gravity thereafter diminish, and anuria, azotemia, and death may follow. Recovery occurs during the second or third week, and renal function usually returns to normal after some delay (see Chapter 244, section on lower nephron nephrosis). The principal lesions observable in the kidneys are obstruction of the renal tubules by pigmented casts, and necrosis of the epithelium of the distal convoluted tubules. The underlying mechanism may be vasoconstrictive renal ischemia. The action of a toxic substance has been suggested.

A very similar syndrome may follow extensive burns of the skin, the ingestion of highly toxic agents, severe intravascular hemolytic crises such as follow transfusion of incompatible blood, or reactions to sulfonamides and other drugs.

Finally, it should be pointed out that other changes probably take place in response to injury which so far have not been studied or defined as clearly as those which have just been discussed. Thus it is possible that the renal vasoexcitor material VEM and the hepatic vasodepressor VDM (ferritin) of Shorr constitute by their opposing actions on the terminal vascular bed a homeostatic system for the regulation of the peripheral circulation which may be disturbed when injury occurs.

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## 34

### Psychologic Reactions to Stress

Henry M. Fox

Childhood Reactions to Environment  
Sleep and Dreaming  
Denial of Reality and Repression  
Incorporation  
Projection  
Introjection  
Imitation and Identification  
Summary

Environmental demands elicit a kind of response which can be distinguished from the way in which the organism reacts to inner drives, and there is a certain practical value in differentiating external from internal stress. But external stress is never experienced as purely external, and even the most extreme threat from the outside is perceived in terms of the individual's experience with similar threats in the past.

**Childhood Reactions to Environment.** During infancy and childhood there is a very incomplete separation of what is felt to arise from within, from that which seems to originate outside the person. At birth, for instance, stress results from the change in environment from the womb to the outside world, but the infant has no concept of himself as an individual distinct from his surroundings, and birth itself constitutes the beginning of his education in this regard. It is only with the passage of the months and years that he gradually discovers himself as an individual capa-

ble of appreciating an environmental alteration as such.

The infant leaves behind him the warmth and darkness and steady nutrition of the womb, and at the moment of birth his entire organism is activated by stimuli coming in from every avenue of sensual perception. As the baby emerges from the birth canal and first fills his lungs with air, he is suddenly exposed to the world of light, sound, smell, and touch. In states of anxiety the flood of sensations from the surface of the body, as well as from end organs of the autonomic nervous system within the viscera, are also passively perceived, and the quantity of stimulation may be so great as to result in painful distress. Full-fledged anxiety is experienced as an organism-wide reaction which involves every physiologic system of the body, including the central nervous system. Although later in life certain fairly specific patterns may become characteristic for a certain individual, the effect of anxiety on respiration, heart rate, and blood pressure, the changes it brings about in peripheral and internal circulation, the alterations produced in the function of the gastrointestinal tract and in genitourinary function, as well as the transformations in thought and feel-

ing, exemplify the range of psychobiologic involvement.

The experience of hunger in the newborn infant teaches him a great deal concerning his separateness as well as his dependence on the mother who feeds him. The intense inner distress which he feels when he is hungry can be allayed only by receiving food through his mouth from his mother or whoever takes the mother's place. If his hunger is left unsatisfied for any period of time, his distress and anxiety become overwhelming. Being held in the comforting security of his mother's arms, being fed enough milk to satisfy his hunger, and falling asleep thereafter come closest to reproducing the conditions of the womb, where anxiety is presumably at a minimum.

**Sleep and Dreaming.** Throughout life the individual attempts to deal with anxiety in ways which, in a sense, are developments and elaborations of this early maternal reassurance. Each night the sleeper retreats to a kind of fetal state and gains some respite from the perceptions and demands of the outer world. External reality can be shut out fairly effectively during sleep, but the uprush of past memories and instinctual urges threatens to reach motor expression and destroy sleep, unless kept in check by the complex mechanism of dream formation. The brilliant researches of Sigmund Freud have shown us how to read the apparently "senseless" dream pictures as code symbols by means of which the latent dream thoughts gain disguised expression and so permit sleep to proceed without interruption. Nightmares represent a breakthrough of impulses which are too forceful to be handled by the ordinary dream defenses. Study of the dream process has revealed that the "senselessness" is only apparent and that the dream phenomena actually are produced according to a primitive kind of logic which is quite different from ordinary common sense. The time sequences of waking experience, for instance, lose all meaning, and events of the distant past seem to happen alongside of what occurred only yesterday. Spatial separations vanish and places which may be thousands of miles apart seem closely juxtaposed; ideas may be represented by their diametric opposites, or, by a curious process of condensation, one image may become the representative of a whole series of feelings and experiences. This strange, primitive world of

dreams becomes reality during sleep, and constitutes a normal kind of regression which has important similarities to the more permanent states of regression manifested clinically as psychosis, to which the individual retreats when his other defenses have broken down.

**Denial of Reality and Repression.** Sleeping and dreaming thus alter the state of consciousness and protect the individual from external and from internal stress. Other alterations in consciousness perform a similar function. When the capacity for differentiation of the outside world has developed sufficiently, it becomes possible to focus the attention in a selective fashion. This requires the capacity to ignore perceptions peripheral to the area of interest and, temporarily at least, to detach present experience from the irrelevant past. These functions may become so highly developed that the stream of consciousness becomes more or less permanently dispersed. Blind spots for unwelcome aspects of external reality become established because of the need to deny the existence of truth which is too painful to accept, and a whole series of past experiences may sink into amnesia because the emotions generated by remembering them are too disturbing. The analogous mechanism of repression serves to prevent threatening instinctual urges from welling up into consciousness. When defense mechanisms such as denial or repression become too well entrenched, they may interfere seriously with the capacity for adaptation to external reality, or may result in a disabling depletion of instinctual energy.

Sleep, denial of reality, and repression of instinctual urges all protect the organism by what might be described as a partial paralysis of certain functions. An attack of vasovagal syncope is a dramatic example of this type of defense. The person reacts to powerful unconscious fears provoked by the sight of flowing blood, for instance, by a loss of consciousness which shuts off further perception. Other clinical examples include the whole range of hysterical dissociations: from limb paralysis to loss of the power to phonate, from blindness to sexual frigidity, and from fugue states to losses of memory.

**Incorporation.** There are also more active ways of dealing with stress and distress. The hungry infant responds with a reflex tropism to a touch on his cheek, and begins to suck when he feels the nipple in his mouth. This is his primary rela-

tionship to the world outside himself and it is completely somatic. To the infant his mother's breast is equivalent to his mother herself, and actually all that he needs from the outside world is represented by the nipple he is sucking. Thus, his first attempts toward active mastery of the environment consist of somatic incorporation in an entirely literal sense. In psychotic states, such as schizophrenia, there is a regression to this primitive kind of interpersonal relationship. A schizophrenic woman, for instance, picked up a carnation, chewed it up, and swallowed it. She associated the carnation with her mother's breast and she began talking about how much she hated her mother. Devouring the carnation thus meant a destructive incorporation of her mother in a curiously literal sense similar to the experience of the infant. Ernst Simmel has pointed out that the same sort of mechanisms provide the psychologic basis for chronic alcoholism. One patient became aware that his manner of draining his bottles of whisky to the last drop was a compulsive imitation of what he had long ago seen his baby brother do when being fed from a bottle by their mother. The whisky, for this patient, evidently had become a substitute for the milk of infancy, and for others the alcohol symbolizes the mother herself in the same primitively literal sense as has been indicated above. As Simmel states, "By drinking her, as it were, he becomes one with her and thus approximates psychologically a return to the womb." The mother for whom the alcoholic longs is often hated as much as she is wanted because she exploited the patient's need for dependence when he was a child and had no genuine interest in helping him to grow up and stand on his own feet. Simmel states that all his alcoholic patients had a deep-seated hatred for their mothers which was deeply repressed as an impulse to incorporate, to destroy, the mother by devouring her.

**Projection.** Later the baby learns to swallow what is good and spit out what is bad, but these are also the processes by which he is learning to differentiate himself from the outside world. He tests objects by bringing them to his mouth and thus learns to recognize their relative resistance to incorporation. The internalization of that which is "good" and strengthening and the externalization of what is foreign or dangerous provides a basic pattern which later is elaborated in many

different ways. By means of the well-known pathologic defense mechanism of projection, for instance, disturbing inner impulses are attributed to other persons in the environment, thus relieving the patient of any responsibility for such feelings. The jealous husband, for instance, has very often projected onto his wife his own impulses to be unfaithful. As Freud first pointed out in his studies of paranoia, delusional projection may protect an individual from the recognition of impulses of an even more disturbing nature. The man who has unconscious homosexual impulses, for instance, may develop pathologic jealousy concerning his wife as a means of denying his unconscious homosexual attraction to her supposed lover. In other words, his jealousy is a way of denying the unacceptable "I (a man) love him (another man)" by substituting the situation, "It is not I who love him but she does."

**Introjection.** Introjection, which is the opposite of projection, is a psychologic process by means of which the person may defend himself from the pain of losing a precious external object by internalizing it. Normal mourning and bereavement illustrate the way in which this kind of defense becomes operative. When a cherished person dies, the mourner develops an intensely vivid image of the lost person within himself. He is often able to imagine his features more easily than he could when the person was still alive, and may feel especially close to him. The mourner becomes so much preoccupied with this internal image that momentarily he may even believe that he actually sees the person he has lost on the street, until he realizes that he has been looking at a stranger who has some similarity of form or feature; or he may have an almost hallucinatory experience of thinking he sees the lost person sitting in his accustomed chair, which now is really empty. This process helps to cushion the shock of the bereavement, and gradually, as the days and months pass, various memories of the beloved person come to mind and the grief is, in a sense, spread out into numerous partings which cause pain to the individual in doses which he can digest. Where there have been too many hostile feelings toward the lost person, the process of internalization may be more like the destructive incorporation described above. The normal process of mourning does not take place, and, instead of the gradual detachment of the affectionate investment in the living person who has now

been lost, the mourner may become pathologically depressed with much self-blame and self-devaluation. Freud was the first to point out that these self-attacks are really aimed at the unconsciously internalized object, usually a parent, who was loved, lost, and hated long ago. The most extreme example of such aggression turned against the self is suicide. Suicidal attempts in persons with reactive depressions are often carried out in a way that clearly demonstrates the intention to punish someone else who will "then be sorry." In full-fledged melancholia the "someone else" is the parental image which has been introjected and destroyed.

Introjection and projection are primitive mechanisms, and in many ways they are close to magic. The belief in the efficacy of swallowing a love potion illustrates the primitive conviction that the incorporation of certain material substances confers the power to command the submission of the love object. More ordinary examples of the unconscious persistence of the belief in oral magic are the half-humorous rumors in most summer camps that "they" have put salt-peter in the food to dampen the sexual urges of the campers, the widespread conviction in the Army during the war that quinacrine ("Atabrine") produced sterility, or some of the pseudoscientific folklore concerning the effects of vitamins and hormones.

**Imitation and Identification.** It is only when a certain degree of maturity has been reached that the individual is able to give up the pattern of mastery by incorporation and, instead, to seek strength by imitation and identification with admired persons outside himself. Mastery of the instincts and social learning arise from the possibility for affectionate identification with the parent. Men under stress derive great strength from the capacity to identify themselves with their leaders. There were many examples during the war where bomber crews or front-line infantry units withstood external stress of unbelievable severity as long as the personal feeling of identification with the pilot or with the company commander was maintained. Loyalty to abstract ideals such as democracy seemed remote and even irrelevant in the thick of combat, where the only reality was the close bond with the other men of the outfit. If for some reason a man was shifted away from his own unit or the unit was broken up because of excessive casual-

ties, the effect on the morale of the individual was very destructive. In some of the fighter pilots, a psychologic identification with the airplane itself seemed to take place. The plane was believed to be almost magically indestructible, and the pilot felt that no harm could possibly come to him as long as he was inside it. After the plane had been hit a few times by flak, this protective identification lost its magic and the pilot suddenly felt intensely vulnerable.

As long as the individual feels self-sufficient and strong enough to cope with an external threat, his feelings of fear mixed with anger are directed against the enemy. Physiologically and psychologically, the organism gets ready to fight or to run away. The imminence of danger is signaled by a feeling of apprehension which results in a sharpening of the senses. The individual becomes alert and responsive to the faintest crackling of a twig which may mean that the enemy is coming closer. The physiologic preparedness for action has been well described and includes a quickening of the heart beat, faster breathing, a rise in blood pressure, and increased tone in the muscles of the extremities, as well as the biochemical preparedness in which epinephrine and other humoral substances play an important role. It is only when the individual feels that he is completely helpless that the biologically useful alerting function of anxiety passes over into pathologic distress. This was well illustrated during the retreat at Dunkirk, where severe anxiety developed in men who had previously fought bravely against overwhelming odds. The severe anxiety resulted from the fact that during the retreat there was no possibility of fighting back, and this greatly increased the sense of helplessness. During the bombings of London it was found that as long as an individual was able to direct his energies to the performance of some useful task, such as helping others to get down into the bomb shelters, the feelings of helpless anxiety tended to disappear. When there is no possibility for taking effective action, the feeling of helplessness re-establishes the psychologic situation of infancy, and the person tends to react according to some of the more primitive patterns which have been described above.

A very striking example of such behavior is the so-called startle reaction, which developed in some of the soldiers who had lived through par-

ticularly severe experiences of bombardment. The alerting mechanisms had become pathologically caricatured, and the creak of a board in a base hospital many miles behind the lines, for instance, would produce a violently exaggerated reaction in the soldier, who would throw himself out of bed to the floor in an almost reflex fashion. Grinker and Spiegel describe the neurophysiologic basis for this reaction in terms of the relationship between the higher cortical centers (the cerebral cortex) and the lower centers which integrate, regulate, and reinforce the motor visceral expressions of emotion (the diencephalon). When the individual is excessively fatigued or has been under long-continued emotional strain, his more highly developed integrative activities are weakened, with the result that the archaic and undifferentiated responses of the lower centers escape inhibition. Sham rage following surgical removal of the cortex in an experimental animal is somewhat analogous. In helping a severely anxious patient to regain control of himself, he is encouraged to verbalize his feelings and thus to replace the emotional short cut by consciously integrated thought and activity. Children spontaneously work out methods of mastering their anxieties during play. A child who has been hurt by a needle at the doctor's office, for instance, re-enacts the scene after he gets home, only now he has become the active aggressor and the doll or the teddy bear is cast in the role of the helpless patient. Identification with the aggressor as an antidote to the feeling of helplessness may result in some peculiarly illogical situations, such as those which developed in some of the Nazi concentration camps where, after a period of "adjustment" to camp life, some of the prisoners identified themselves with the S.S. men who were guarding and torturing

them—even attempting to imitate their uniforms as well as their speech and their brutality.

**Summary.** The examples which have been given of the way the human being reacts to stress have illustrated the variety of possible defenses against painful experiences and helpless anxiety. Some of these reactions could be considered largely "psychic," and others are closer to what might be described as an almost "organic" type of reflex. All of them have emotional as well as physiologic implications, and a psychosomatic condition such as duodenal ulcer or bronchial asthma may be interchangeable with states of regressive anxiety or self-accusatory depression. From the standpoint of health, the evaluation of any given pattern of defense against stress depends upon whether the adaptation to external reality is impaired or improved, and upon the degree to which instinctual energies are sublimated into socially constructive activities.

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## Principles of Immunity

B. V. Jager

Introduction
Antigens
Antibodies
Complement
Antigen-Antibody Reactions <i>in Vitro</i>
Antigen-Antibody Interactions <i>in Vivo</i>
Final Considerations

### INTRODUCTION

In this section it is proposed to review certain fundamental principles of immunity and to give emphasis to those that seem directly applicable to an understanding of diagnostic and therapeutic measures employed in clinical medicine.

Much of our present knowledge of immunity is based upon a study of antigens, antibodies, and their interactions *in vivo* and *in vitro*. In a broader sense, however, immunity depends upon all of the principles responsible not only for the protection of the individual from infectious diseases but also for recovery from such diseases. Chilling, excessive fatigue, nutritional deficiencies, and concurrent debilitating diseases may play important roles in influencing the susceptibility of the host to infection. The virulence of the invading organisms, the size of the inoculum, the portal of entry, the site of its localization in the host, and the presence or absence of sufficient circulating leukocytes may be determinants in the control of infection. Other properties intrinsic in the host as well as in the invading agent may assist in the spread or localization of infection.

The discussion which follows is concerned largely with the nature of antigens and antibodies and their interactions. The immunologic principles operating in hypersensitivity are considered in a subsequent section (Chapter 36).

### ANTIGENS

**Definition.** Antigens are substances which, when introduced by suitable routes into animals or into man, give rise to the production of antibodies that are capable of reacting with a high

degree of specificity with the substance administered. Most antigens consist of proteins of molecular weights over 10,000. Many polysaccharides and complexes of lipids, proteins, and polysaccharides are also antigenic.

**Species Specificity.** A number of antigens give rise to antibodies which exhibit species specificity. For example, a rabbit antiserum prepared to human serum albumin will give a visible precipitate *in vitro* with human albumin (the homologous antigen), but will not react with purified horse serum albumin (a heterologous antigen). Similarly, rabbit antisera to whole human serum will not react with antigens present in the serums of most other species. The serums of certain apes, however, do show antigenic similarity to human serums.

**Tissue Specificity.** Specificity also extends to the separate blood and tissue components of the host. For example, the antiserum prepared in the rabbit to human serum albumin will not react significantly with the gamma-globulin fraction of human serum. Proteins such as hemoglobin, thyroglobulin, and certain muscle proteins of man or of animals give rise to antibodies which react only with the type of blood or tissue antigen used to prepare the antiserum. Not all body proteins, however, show these striking antigenic specificities.

**Variations in Antigenicity.** For reasons that are not well understood, certain proteins stimulate greater antibody production than others. Thus, in the rabbit, human gamma-globulin causes more antibody formation than does human hemoglobin. Sometimes the antibody response may be improved by varying the state of the antigen administered. Alum-precipitated diphtheria toxoid has been found to produce higher antibody titers than an equal amount of the soluble toxoid. It has been demonstrated that certain poor antigens produce greater amounts

of antibody when they are administered in an oily suspension or are mixed with killed tubercle bacilli or Gram-positive cocci. Substances employed in this way to enhance antibody formation are termed *adjuvants*. Their mode of action seems to result in part from continued slow release of antigen into the host. It has been suggested that the local tissue reactions at the site of antigen administration also may stimulate antibody formation.

**Modification of Antigens.** Treatment of proteins by various physical and chemical means may alter their structure so that the antibody produced to the altered protein may react little or not at all with the unaltered protein antigen. On the other hand, certain bacterial toxins such as diphtheria and tetanus toxins, when permitted to stand for several weeks in a suitable concentration of formalin, become modified so that their toxicity is lost, yet these altered toxins (toxoids), when employed as antigens, stimulate formation of antibodies capable of neutralizing the unaltered toxins.

**Bacterial Antigens.** Bacteria are found to contain multiple antigenic substances, each of which is capable of stimulating production of specific antibodies. Many bacteria also elaborate soluble protein substances, some of which possess high toxicity (exotoxins). In recent years improved physical and chemical fractionation methods applied to bacteria and their products have yielded many purified antigenic substances. Investigations with these specific fractions rather than with whole organisms have contributed greatly to our knowledge.

Certain relatively pure protein or carbohydrate fractions from bacteria, when injected into animals, have been found to protect the animals against subsequent infection with whole virulent organisms. Thus, the type-specific pneumococcal polysaccharide, the type-specific meningococcal polysaccharide, and the type-specific *M* protein of the beta-hemolytic streptococcus, when employed as antigens, stimulate production of antibodies which protect animals against subsequent infection with the whole virulent organisms. In man, vaccination with type-specific pneumococcal polysaccharides was shown to confer protection against pneumonia of the corresponding specific pneumococcal types. Although giving rise to demonstrable antibodies, other fractions, however, fail to confer protection.

The realization that one or a few of the many antigens present in a bacterium may be concerned with protection permits some understanding of the discrepancies that have been observed when agglutinating antibody titers to bacteria are compared with neutralizing antibody titers. It is readily understandable that the content of protective antibody in a given antiserum may be low while antibodies to other bacterial antigens may be high. Similarly, the presence of agglutinating antibodies in the serums of patients during certain bacterial infections may be demonstrable in the absence of protective antibodies.

Bacterial fractionation facilitates the identification of specific types of certain bacteria. Frequently, however, the typing can be accomplished without fractionation if suitably absorbed antiseraums are available. An antiserum prepared in the rabbit by injection of type 2 pneumococci will agglutinate other types of pneumococci. If large numbers of pneumococci of another type, such as type 3, are added successively until further addition of organisms fails to produce agglutination, the antiserum, thus absorbed, will react only with type 2 pneumococci. Purification of certain substances contained in or produced by the beta-hemolytic streptococcus has offered a useful investigative tool in the demonstration of the somewhat altered antibody response to certain streptococcal products in patients with acute rheumatic fever. As an illustration, in the patient with a beta-hemolytic streptococcal infection, antibodies may be demonstrated to the streptococcal *M* protein, the *T* protein, hyaluronidase, desoxyribonuclease, streptolysin *O* and *S*, streptokinase (fibrinolysin), and the erythrogenic toxin. In the rheumatic subject, certain of these antibodies tend to be present in greater amounts than in the nonrheumatic subject who has had a beta-hemolytic streptococcal infection.

**Simple Haptens.** Many simple chemicals are incapable of stimulating antibody production upon injection into animals or man. Yet these substances, when coupled to proteins, lead to the production of antibodies which may show high specificity for the groups introduced into the protein molecule. These substances are termed *haptens*. As an example, sulfanilic acid may be coupled to a protein by means of the diazo reaction. An antiserum prepared against sulfanilic acid coupled to human albumin would produce a

precipitin reaction in vitro with an antigen prepared by coupling sulfanilic acid to ovalbumin, even though antiserum to human albumin alone could not react with ovalbumin. The specificity here is conferred by the small chemical group introduced into the protein molecule. The simple hapten, when added to specific antiserum, usually does not give a visible reaction such as precipitate formation. However, the subsequent addition of hapten coupled to protein to this system likewise does not lead to a visible reaction. The previously added simple hapten has combined specifically with the antiserum, and thus has blocked its reaction with the subsequently added coupled hapten. To return to the example cited above, addition of sulfanilic acid alone to the antiserum produced by injection of sulfanilic acid coupled to human albumin would not result in formation of a precipitate. Nonetheless an interaction has occurred, since the subsequent addition of sulfanilic acid coupled to ovalbumin would not give the precipitate formation that would have been obtained had the sulfanilic acid alone not been added previously.

**Complex Haptens.** Hapten groups vary greatly in complexity and also in their degree of specificity. Some complex haptens will produce visible flocculation or complement fixation, or even in vivo reactions, in the presence of specific antibodies.

Certain haptens are distributed widely in animals and in bacterial species. An example is the *Forssman substance*, which is of importance in the heterophil agglutination test. When suitably injected, alcoholic extracts of tissues or of erythrocytes of many animal species, and extractions of certain bacteria, will lead to the production of antibodies capable of agglutinating sheep erythrocytes. Such sheep cell agglutinins are termed *Forssman antibodies*. These tissue extracts constitute haptens rather than complete antigens, since the alcoholic extracts alone usually do not stimulate antibody formation unless they are mixed with a foreign protein. In this case simple mixture rather than an organic reaction such as the diazo coupling is sufficient. Not all Forssman antibodies have identical characteristics. For example, the sheep erythrocyte-agglutinating antibody that appears in human serum in infectious mononucleosis does not react with guinea pig kidney but does react with beef erythrocytes. In these respects it differs from the sheep eryth-

rocyte-agglutinating antibody that may be present in the blood of patients with serum sickness.

Another illustration of a complex hapten is the Wassermann antigen, a lipid (cardiolipin) which is present in alcoholic extracts of many animal tissues, especially heart muscle. It reacts with an antibody present in the serum of patients with syphilis. The exact origin of the antigenic stimulus for producing Wassermann antibody in the syphilitic patient is not known. It cannot be determined whether the treponeme synthesizes this substance in effective antigenic form or merely furnishes a foreign protein which renders antigenic the hapten from host tissue. It is well recognized that, under special circumstances, a similar type of antibody may be present in the serum of nonsyphilitic patients, leading to so-called false positive serologic tests for syphilis.

## ANTIBODIES

**Origin and Nature.** Antibodies are modified globulins which usually appear in the serum of the host following injection of antigens by a suitable route. In man, nearly all antibodies occur in the gamma-globulin fraction of the serum. In certain other animal species, antibodies may be found in other globulin fractions in addition to the gamma-globulin fraction. Administration of antigens to man or to rabbits leads to an increase in the quantity of serum gamma-globulin. Part of the increase in this fraction following immunization results from increase in specific antibody, while another portion—and often the greater amount—is derived from an increase of gamma-globulin which cannot be shown to consist of specific antibody. Heating of serum to 56° C. for 30 minutes, the method used to inactivate complement, does not inactivate antibodies. At slightly higher temperatures, however, certain antibodies are destroyed more rapidly than others. This phenomenon has limited diagnostic value and occasional usefulness for identification and separation of antibodies.

**Site of Antibody Formation.** The experimental evidence that existed until the last decade suggested that antibodies were formed largely by the reticuloendothelial tissues. Since that time, the problem has been reopened and has been the subject of extensive investigation. Some workers regard the lymphocyte as the primary site of antibody formation, but the subject is still unsettled. When particulate antigens such as sheep

erythrocytes, whole bacteria, or influenza virus are injected into the feet of small animals, antibodies may be demonstrated in the regional lymph nodes before they appear in the blood. During the early period of antibody formation, the antibody titers present in extracts of lymphocytes from regional lymph nodes are found to be higher than the titers in the circulating blood. Several investigators have presented evidence that the plasma cells rather than the lymphocytes are the site of antibody formation. Their work suggests that the plasma cells originate from reticuloendothelial cells. Further investigation has been stimulated by the observation that adrenal cortical extract administered to man or animals produces a lymphopenia in the circulating blood. In animals, lysis of lymphocytes also was noted in the lymph nodes and spleen. If antibodies are contained in the lymphocyte, it might be supposed, therefore, that administration of adrenal cortical extract would lead to prompt increase in circulating antibody titers. This concept became even more attractive when it was demonstrated that many types of noxious stimuli incite secretion of adrenocorticotropic hormone. This in turn should lead to increased release of adrenal cortical hormone. On the basis of such a hypothesis, an excellent explanation could be derived for the nonspecific anamnestic reaction that is observed occasionally after various types of body injury such as fever, hemorrhage, tissue destruction, and exposure to cold. Unfortunately, the bulk of the current evidence suggests that administration of adrenal cortical hormone to man and animals fails to cause significant increases in existing antibody titers. The same finding obtains after the adrenal cortical hormone release subsequent to injection of adrenocorticotropic hormone. In addition, it has been shown that destruction of lymphocytes by x-ray irradiation and by the nitrogen mustards does not produce a sudden rise in existing antibody titers. It might be postulated that the failure to observe increased titers is due to the fact that the antibody released from the lysis of lymphocytes is rapidly destroyed. However, certain evidence suggests that rapid antibody destruction does not occur after adrenocorticotropic hormone administration or after administration of adrenal cortical extract. The site of antibody formation is therefore not clearly established. Factors such as species variation, varia-

tions resulting from dissimilar types of antigens, and lack of sufficiently quantitative antibody determinations may account for some of the discrepancies.

**Routes for Antigen Administration.** Antibodies may be produced not only by parenteral administration of antigen but also occasionally by intranasal instillation, inhalation, ingestion, and even by contact with the skin and mucous membranes. These additional routes have particular significance in certain types of human hypersensitivity reactions (unfavorable antigen-antibody interactions in man).

**Anamnestic Reaction.** When an animal is immunized for the first time with an antigenic protein, circulating antibodies usually appear within four to five days and the maximal antibody titer is obtained within seven to ten days. The titer thereafter falls, either slowly or rapidly, so that circulating antibody may still be present at the end of six months or may be absent after six weeks. When such an animal, after a delay of one or several months, is given a new injection of the same antigen, the formation of antibody is accelerated, the peak titer usually appearing several days earlier than following the initial injection. The maximal titer usually is also higher and the decline in antibody titer less rapid than was observed after the initial injection. This accelerated reaction to the new administration of the same antigen is termed the *anamnestic reaction*. When intact bacteria are employed as antigens, the response to the initial injection is similar to that obtained with the less complex antigens. Here, however, subsequent readministration of the same bacteria usually does not lead to accelerated antibody production. Nonetheless, the antibody titers obtained with the new injection usually are higher than those after the initial injection.

**NONSPECIFIC ANAMNESTIC REACTION.** Under the term anamnestic reaction is also included a different phenomenon. Certain traumatic procedures, such as venesection, injection of a foreign protein, or administration of toxic metals, may produce in the host an increase in antibody titer to an antigen which had been received much earlier. In controlled experiments in animals this response is inconstant. The importance of the phenomenon may have been exaggerated in early studies based on crude quantitative methods. Its mechanism is not understood. The possible rela-

tion of this response to lymphocytolysis by adrenal cortical hormone subsequent to pituitary stimulation with release of adrenocorticotrophic hormone has been discussed already. Clinically this concept is employed to account for the rises in antibody titers to certain bacteria, such as *Salmonella typhosa*, *Brucella abortus*, and *Pasteurella tularensis*, that may be observed long after the initial infection, when the host is subjected to a new bacterial infection such as pneumococcal pneumonia or beta-streptococcal pharyngitis.

**Factors Influencing Quantity of Antibody Production.** Both qualitative and quantitative methods for estimation of serum antibody content are available. The amount of antibody produced in the serum of an immunized host depends upon the nature of the antigen, the animal species employed for immunization, the route of antigen administration, the number and size of injections, the total amount of antigen introduced, the presence or absence of previous exposure to the same or a related antigen, and upon the *individual animal*. It might be supposed that, when a number of antigens were administered simultaneously into a given host, the antibody response to each individual antigen would be less than if only a single antigen had been given. Actually this is found to be the case when 20 or more antigens are injected at once into an experimental animal. However, when only three or four immunizing agents are given simultaneously to human subjects, the antibody response here to each individual antigen is at least as good as if each one had been administered at intervals. Thus infants and children frequently are given pertussis vaccine and tetanus and diphtheria toxoids at the same time.

The quantity of antibody that is present in the serum at any one time depends upon the amount of antibody that is being produced in the tissues, upon the factors controlling the release of this antibody into the blood, and upon the rate of destruction of the antibody that is formed.

Some approximation of the rapidity of antibody destruction may be obtained by injecting specific antibody from one animal into another animal of the same species. Passively transferred antibody usually has a half-life of about one week. With the isotope technic it has been demonstrated that labeled amino acids administered to actively immunized animals during the phase

of decreasing antibody titer become incorporated into specific antibodies. This is interpreted to indicate that antibody production is proceeding, but that antibody destruction is occurring at a more rapid rate.

The great individual variation in quantity of circulating antibody produced after administration of a given antigen deserves emphasis. In certain individuals no demonstrable circulating antibodies to a specific organism appear during or subsequent to infection or following administration of vaccines. For example, only 85 per cent of individuals with beta-hemolytic streptococcal infections develop antibodies to the bacterial hemolysin. Certain patients with typhoid fever and with brucellosis never develop circulating antibodies. The explanation for this is not known.

Deliberate measures to inhibit antibody production have been employed. Exposure to large doses of x-rays, repeated injections of nitrogen mustard, and even large doses of salicylates suppress circulating antibody titers in experimental animals. Starvation, protein depletion, and nutritional deficiencies also may reduce antibody titers.

**Sources of Antibodies in the Host.** These are of three types:

1. ACTIVE IMMUNIZATION. Antibodies develop in the host as a result of contact with specific antigenic substances. Such antigens may have arisen in natural infections or may have been introduced into the host in the form of vaccines.

2. PASSIVE IMMUNIZATION. Antibodies formed in a donor host may be passively transferred into a recipient host. In man, transfer of maternal antibodies to the fetus occurs through the placental circulation. Very little antibody is transferred to the offspring in man by way of the colostrum or milk of the mother. Artificial transfer of antibodies may be effected by introduction of antibody-containing serum into the circulation of the recipient.

3. NATURAL ANTIBODIES. These appear in the serum of the host in the absence of any known previous contact with specific antigens. These antibodies usually are of low titer and are capable of reacting with certain bacteria and with animal erythrocytes with considerable specificity. Moreover, the isoagglutinins present in man appear to arise without previous antigenic stimulation. The origin and nature of natural antibodies is not clear. Some investigators be-

lieve that these antibodies do arise spontaneously and are not identical with acquired antibodies. In certain instances, however, the presence of "natural" antibodies may be explained by assuming that the host has been exposed to hapten substances from various sources such as the bacterial flora of the nose, mouth, and gastrointestinal tract. Certain of these organisms can stimulate production of antibodies cross reacting with "natural" antibodies.

**Autoantibodies.** Under ordinary circumstances the host cannot make antibodies to his own blood or tissue constituents. However, exceptions occur with tissue antigens that do not ordinarily reach the circulation. For example, injury to the uveal tract in one eye may lead to "sympathetic" ophthalmitis in the uninjured eye. It is assumed here, with suggestive proof, that the injured uveal tract tissues stimulate production of antibodies capable of reacting with the uninjured tissue of the other eye. The antibody reacting with the uninjured uveal tissue leads to tissue injury. Such mechanisms have been suggested to explain the renal injury in acute glomerulonephritis, the cardiac damage in acute rheumatic fever, the brain tissue injury in multiple sclerosis, and the occurrence of certain types of hemolytic anemia.

### COMPLEMENT

Fresh human and animal serums contain a labile factor designated as complement. In the presence of complement, antibodies to red blood corpuscles usually produce hemolysis of added erythrocytes. Complement facilitates the death and dissolution of certain bacteria in the presence of specific antibody. The addition of complement to specific immune serum enhances phagocytosis of bacteria by leukocytes introduced into the system. This substance decreases in serum which has been permitted to stand even a few hours at room temperature. It disappears rapidly (within 30 minutes) from serum that has been heated to 56° C.

Complement actually consists of at least four components, designated by the terms C'1 to C'4. These substances have been obtained in concentrated form from serum, and either consist of protein molecules or are substances carried by proteins.

By quantitative techniques the amount of total complement and of each of the four fractions in

serum can be determined. While it is clear that complement must have a significant role in immunity, studies of its variations in disease have been rather disappointing and have not yielded the clear correlations that have been observed with quantitation of antibodies or alterations in leukocytes.

In vitro, many antigen-antibody interactions bind complement. Once the complement has become bound, it is no longer available for further action. This principle is the basis for the complement-fixation technic.

### ANTIGEN-ANTIBODY REACTIONS IN VITRO

Much of our knowledge of antigens and antibodies and many diagnostic immunologic tests depend upon studies of reactions of antigens and antibodies in the test tube. Depending on the physical state of the antigen and at times upon the presence or absence of complement and of leukocytes, these reactions may assume different forms. Thus it may be shown that the antibody produced to a type-specific pneumococcal polysaccharide will give a precipitin test with this carbohydrate antigen, will produce agglutination of whole pneumococci of the same type, will bind complement when either the polysaccharide or whole bacteria are added, or will enhance phagocytosis of whole living bacteria in the presence of leukocytes.

**Precipitin Test.** When soluble protein antigens or polysaccharide antigens are added to their specific antisera, there usually appears a fine flocculation or precipitate. If the antigen is layered carefully over the antibody, a ring of precipitate appears at the interface between the two fluids. The precipitin titer of an antiserum may be approximated crudely by determining the highest dilution of an antigen that will still give a visible precipitate when added to undiluted antiserum or, conversely, by determining the greatest dilution of antiserum that still will react visibly with a fixed quantity of antigen. The latter method has been found to give a more quantitative approximation. Even here with the two-fold dilution technic, the titer of a single sample of antiserum may vary one or two tubes with repeated determinations. With *homogeneous* proteins or polysaccharides it is possible to determine quantitatively the amount of antibody present in a given antiserum and to express this

value in milligrams of antibody or antibody N per milliliter of serum. This procedure is based on successive additions of antigen to the anti-serum until precipitation is complete. The precipitate is removed by centrifugation, washed, and its nitrogen content determined. When necessary, a correction is made for the small amount of antigen nitrogen in the precipitate. The content of the specific antibody can be calculated accurately.

The quantitative precipitin technic has contributed greatly to our knowledge of antigen-antibody interactions. Antigens and antibodies combine in different proportions depending on the relative concentration of each. For example, in the circumstance where the number of antibody molecules present is far in excess of the number of antigen molecules in the system made up of chicken ovalbumin and its homologous rabbit antiserum, five molecules of antibody are bound to each molecule of ovalbumin. In the zone where there is no excess of antigen or of antibody (zone of equivalence), the ratio of antibody molecules to antigen molecules is approximately three to one. When a great excess of antigen is present, still fewer molecules of antibody are attached to each molecule of ovalbumin and the complex becomes soluble. The presence of antigen excess, of antibody excess, or of equivalence in the system may be demonstrated by examining the supernatant fluid after removal of the precipitate by adding to one aliquot a small quantity of antigen and to another a small quantity of antiserum. Thus, if the supernatant fluid reacts with antigen and not antibody, the original precipitate must have been made in the zone of antibody excess.

The formation of the precipitate may be explained by assuming that the polyvalent antigens bound to divalent antibody globulin molecules form lattice structures which ultimately become large enough to form visible aggregates. As already indicated, when a large excess of antigen is present in the reacting system, no precipitate occurs. This is due to the formation of soluble antigen-antibody complexes. In certain instances, particularly toxin-antitoxin reactions, not only is there no precipitate visible in the zone of the antigen excess, but there is also none at the zone where antibody is present in excess.

In general, precipitin titers in human serum, as measured by serial dilutions of antigen or anti-

body, are not high. At times the sensitivity of the system may be augmented by the addition of lipoid or collodion particles which presumably become coated with antigen. These larger particles, when interlaced with relatively few molecules of antibody, form aggregates that are visualized more readily.

**Agglutination Tests.** When whole living or killed bacteria are added to specific antiseraums, clumping of the bacteria occurs. Because of the relatively large size of bacteria as contrasted to that of protein molecules, relatively few organisms interlaced with a few antibody molecules form visible clumps. Thus, in general, agglutinin titers as measured by serial dilution of antibody-containing serum plus a constant quantity of organisms show higher titers (visible clumps at greater dilution of antiseraums) than are encountered in precipitin tests. The limited accuracy of the ordinary agglutination test, as carried out with serial twofold dilutions of antiserum, deserves emphasis. The same test performed in the same laboratory on the same antiserum will fluctuate in titer from day to day, frequently by one or occasionally by two twofold dilutions. When the same test is performed in different laboratories, greater fluctuations may be expected. Under specified conditions, the amount of agglutinating antibody in an antiserum can be measured quantitatively by using methods similar to those employed in the quantitative precipitin technic. The potency of commercial therapeutic antiserum to the *type B influenza bacillus* is now expressed in milligrams of bacterial antibody agglutinating protein nitrogen rather than in the biological units that were employed formerly.

**Antibodies to Red Blood Corpuscles.** Antibodies to erythrocytes usually are classified as hemagglutinins or as hemolysins. Hemagglutinins are substances which produce clumping of red blood corpuscles in vitro. Quite apart from specific antibodies, red corpuscles may be clumped by various plant substances, including ricin and certain chemical substances, and by certain viruses (for example, mumps virus and influenza virus). The isoagglutinins of human blood are antibodies which are normally present in the serum of subjects of certain blood types and are capable of clumping erythrocytes from subjects of a blood type different from the serum donor. These presumably constitute natural

antibodies. Occasionally, in man, antibodies arise which are capable of clumping the individual's own corpuscles. These are termed *autoantibodies*. They may appear in certain types of hemolytic anemia. In the serums of patients with atypical pneumonia or less commonly, in the serums of patients with leukemias, *cold agglutinins* may be present. These lead to clumping of the corpuscles of the host or of donor corpuscles of the same blood type when the system is cooled in vitro. In a few patients in whom cold agglutinins have been demonstrated, it has been observed that chilling of a portion of the body such as a single extremity resulted in intravascular hemolysis in the chilled area. Occasional patients in whom cold agglutinins are present exhibit a hemolytic anemia which appears unrelated to chilling. It is not certain whether the cold agglutinins play any role in its production. An Rh- donor transfused with Rh+ corpuscles may develop antibodies capable of clumping Rh+ corpuscles in vitro. These hemagglutinins arise from active immunization of the host.

*Hemolysins* are substances capable of producing lysis of erythrocytes in vitro. Certain bacterial toxins such as the streptolysins of the beta-hemolytic streptococcus and the lecithinase of *Clostridium welchii* lyse red blood corpuscles in the absence of complement. Certain plant substances and certain chemicals in the presence of complement produce lysis of corpuscles, whereas, in its absence, only hemagglutination occurs. Most antibodies to red blood which, in the absence of complement, produce clumping of corpuscles, produce lysis in the presence of complement in vitro. Frequently the quantity of antibody necessary to lyse the cells in the presence of complement is much less than that required to produce hemagglutination. As an example, an antiserum to sheep erythrocytes produced agglutination of red corpuscles in a dilution of 1:256 in the absence of complement. This same antiserum, in the presence of complement, produced lysis of corpuscles when diluted 1:5000. The common identity of hemolysins and hemagglutinins is not absolute. For example, naturally occurring isoagglutinins to certain types of red blood corpuscles produce clumping and little or no hemolysis when complement is present in the system in vitro.

**Complement Fixation.** Minute quantities of antigen reacting with specific antiserum usually

bind complement. This method commonly is employed to detect small quantities of antibody. The serum suspected of containing antibody is heated to 56° C. to inactivate any complement present. To this is then added a known antigen and a measured amount of guinea pig complement. After a specified time, sheep red blood corpuscles and hemolysin (rabbit antiserum to sheep corpuscles) are added to the system. If the initial serum contained antibody specific to the antigen added, it will have bound the complement. When the sheep corpuscles and the hemolysin are added, no hemolysis will occur. If, however, complement is still present, hemolysis will result. Such a hemolytic system affords a sensitive means of detecting whether or not complement has been removed. Complement-fixation tests have merit because of their greater sensitivity in detecting smaller quantities of antigen or antibody than either agglutination or precipitin tests. Insoluble antigens as well as soluble antigens added to specific antiserum may also be expected to bind complement. In the performance of complement-fixation tests, careful controls should be maintained. Complement can be bound or inactivated by substances other than antigen-antibody combinations. Antiseraums or antigens alone which inactivate complement are said to be anticomplementary. An example is the observation that occasional human serums being examined for Wassermann antibody are capable of binding complement in the absence of the cardiolipin antigen.

**Opsonins.** The phagocytosis of organisms by leukocytes in blood in vitro after addition of a suspension of bacteria is facilitated by the presence of specific immune serum (opsonin). Complement also aids in promoting phagocytosis.

**Bacteriolysins and Bacteriocidins.** These are specific antibodies which promote death and sometimes lysis of bacteria in the presence of complement.

**Capsular Swelling.** Certain encapsulated organisms, when brought into contact with type specific antiseraums, develop capsular swelling which may be visualized under the microscope. This is useful in the typing of pneumococci, influenza bacilli, Friedländer's bacilli, and meningococci.

**Monovalent Antibodies.** Available information indicates that most antibody molecules contain two reacting groups, each of which is capable of

combining with an identical portion of an antigen molecule. Most antigen molecules appear to contain multiple groupings of the same type, each of which can bind with an antibody molecule. It is assumed that agglutinates and precipitates in vitro consist of lattice structures resulting from linked antigen and antibody molecules. This concept is supported by studies with simple haptens. The addition of antibodies to haptens does not result in a positive precipitin test when simple hapten is added. If, however, two hapten molecules are coupled to a small organic molecule such as resorcinol, precipitin reactions may occur when the coupled hapten is added to the antiserum, since the hapten is now divalent.

Certain antibody molecules contain only one reactive group, or at least one group is far more reactive than the second one on the antibody molecule in its ability to bind with an antigen. Such an antibody molecule may be expected to bind specifically with the antigen but will not lead to aggregate formation, although after the antibody has become attached to the antigen molecule, the antigen will no longer be capable of combining with a divalent antibody that is added subsequently to the system. In this sense, the univalent antibody constitutes a *blocking antibody*.

In a few specific instances, univalent antibodies have been shown to be of clinical significance. Individuals who are Rh- may become immunized by contact with Rh+ corpuscles either as the consequence of transfusions with Rh+ corpuscles or by the presence of Rh+ red blood corpuscles in the fetus of the pregnant Rh- mother. Since such antibodies may lead to severe transfusion reactions or to fetal injury, it is important that they be recognized. Frequently the serum of such an immunized individual fails to agglutinate a suspension of Rh- corpuscles when the usual in vitro agglutination technic is employed, in which the erythrocytes are suspended in saline and saline is employed for serial dilutions of the suspected antiserum. The antibodies here are behaving as if they were monovalent. Often these antibodies may be detected by adding to the serum suspected of containing antibodies, and to the Rh+ red blood corpuscles, a known agglutinating (divalent) antiserum for Rh+ corpuscles. When "blocking antibodies" are present, the expected agglutination does not take place. The presence of the univalent anti-

bodies may also be revealed by using 20 to 30 per cent bovine albumin or human albumin solution for the suspension of erythrocytes and for serial dilutions of the antiserum in the place of saline.

Another technic for demonstration of these monovalent antibodies is the *Coombs test*. This test for blocking antibodies occasionally will be positive even though the agglutination test carried out in the concentrated albumin solution be negative. For the Coombs test, one employs an antiserum prepared in the rabbit by injecting whole human globulin or human serum. To this is added a thoroughly washed preparation of erythrocytes that have been suspended previously in the serum suspected of containing a monovalent antibody to the erythrocyte. The careful washing will remove human serum particles easily adsorbed to the surfaces of the red blood corpuscles, but will not remove an antibody molecule linked to the corpuscle. The test for monovalent antibody is positive when the corpuscles are clumped by the rabbit antiserum. The test depends on the fact that the monovalent antibody in the human serum is a globulin molecule, presumably gamma-globulin. Antibodies to human globulin present in the rabbit antiserum become attached to the monovalent antibody that is linked to the surface of the erythrocyte. Aggregates are formed so that visible agglutination occurs. Antiserum to human gamma-globulin reacts equally well with human gamma-globulin derived from whole serum and with highly specific antibodies that may be obtained from human serum by various technics. In other words, antibody molecules in human serum, in spite of their own specificity, behave like any other molecule of human gamma-globulin in their reaction with an antiserum to human gamma-globulin.

In certain types of acquired hemolytic anemia in man, the presence of these univalent antibodies may be demonstrated by the Coombs test.

#### ANTIGEN-ANTIBODY INTERACTIONS IN VIVO

**Anaphylaxis.** The reactions of antigens with antibody in the animal are even more varied and complex than those observed in the test tube. Many of these reactions as observed in man are not fully understood. Perhaps the most dramatic in vivo antigen-antibody interactions are those

observed when a foreign protein such as egg albumin is administered to an animal that already has specific antibodies to this antigen as the result of either active or passive immunization. When such an antigen is administered intracutaneously, a prompt cutaneous inflammatory reaction is observed. When the antigen is injected subcutaneously or intramuscularly, a severe local necrotic lesion may occur. If the antigen is administered intravenously, a prompt systemic reaction with death of the animal may ensue. These are variants of the *anaphylactic reaction*. Less well understood are the delayed types of cutaneous and systemic reactions that may occur in animals that are exposed for a second time to complex bacterial antigens. These *in vivo* antigen-antibody reactions are considered in the succeeding chapter.

**Protective Mechanisms.** Less dramatic but of equal importance is the role of antibodies in combating certain types of infectious diseases. For purposes of simplification these will be divided into *toxin-antitoxin interactions*, *bacterial immunity*, and *viral immunity*.

**TOXIN-ANTITOXIN INTERACTIONS.** Certain bacteria elaborate toxic soluble substances (exotoxins) which diffuse readily into the broth of growing cultures. These substances, usually relatively thermolabile, consist of proteins so toxic that parenteral administration of a fraction of a milligram of the purified toxin will often produce death in a small animal.

These toxins show considerable specificity in action. For example, diphtheria toxin primarily injures the heart and peripheral nerves. Among the organisms that produce exotoxins are the following: *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium botulinum*, *Shigella dysenteriae* and *Clostridium welchii*. The beta-hemolytic streptococcus and the staphylococcus each produces several exotoxins with different actions. It is well to note that different strains of the same bacterial species may produce distinctive exotoxins. For example, the exotoxins produced by types A, B, and C of *Cl. botulinum* are immunologically distinct, requiring type-specific antitoxin for neutralization though their pharmacologic actions appear to be similar. Certain nonbacterial substances such as snake venoms and vegetable poisons (for example, the ricin of the castor bean) behave similarly.

Animals may be actively immunized to these

various toxins by such measures as injection of toxin-antitoxin mixtures, or of toxoids (formalin-treated toxins), or by progressively increasing the quantity of exotoxin, beginning with minute non-fatal doses. Once these animals have been immunized, they will be protected even though they receive many thousand times the minimal lethal dose of toxin. The serum of the immunized animals contains antitoxin which may be quantitatively estimated by determining the least quantity of an unknown serum which, when mixed *in vitro* with a known quantity of toxin, will prevent a fatal reaction in a susceptible animal.

Injection of sufficient quantities of antitoxin into a susceptible animal prior to or soon after administration of toxin, will protect the animal. If antitoxin is not administered within a few hours after the toxin injection, no protection is conferred. It would appear that the toxin that has become fixed to susceptible tissues is incapable of neutralization by antitoxin.

In man, antitoxins may be present in the circulation as the result of previous infection with the toxin-producing organism. Such infection may have been recognized or may have been so mild as to escape diagnosis. Antitoxin production also may be induced by parenteral injection or toxoids. Immunization with tetanus and diphtheria toxoids usually confers complete protection against the toxins of these organisms. After toxoid immunization, the height of the circulating antitoxin level and its duration are subject to considerable individual variation. If a previously immunized subject is exposed to infection, his protection should be greater if he is given a new injection of toxoid promptly. The anamnestic reaction in such a case can be expected to result in a somewhat accelerated increase in antitoxin production.

In a nonimmune subject, antitoxin containing serum obtained from immunized animals, or sometimes from patients convalescing from a toxin-producing disease, is employed both prophylactically and therapeutically. In an infection by a toxin-producing organism, antitoxin, if administered in sufficient quantities, will neutralize toxin present in the circulation and toxin that may be expected to appear subsequently as a result of continued absorption from a toxin-producing site. To be most effective, antitoxin must be given parenterally in sufficient amounts and must be given *early* in the course of the disease.

It probably will not neutralize toxin that has become fixed in susceptible tissue.

The immunity to toxins is correlated roughly with the level of circulating antitoxin. The actual amount of circulating antitoxin that is sufficient to protect against the effects of toxin introduced by injection with the toxin-producing organism need not be high. Often only a fraction of an antitoxin unit per milliliter of blood is sufficient. While the actual blood level of antitoxin can be assayed by animal protection experiments, appraisal of immunity to toxins may be determined more easily in certain instances by cutaneous tests in the host. These correlate roughly with circulating antibody titer. For example, both the erythrogenic toxin of the beta-hemolytic streptococcus and diphtheria toxin, when injected in minute quantities intracutaneously in the non-immune host, produce an erythematous reaction. If, however, the host is immune, the intracutaneously introduced toxin is neutralized and no erythema occurs. This cutaneous response forms the basis of the Dick and Schick tests, respectively, for estimating susceptibility or immunity to these toxins.

**BACTERIAL IMMUNITY.** The forces operating to destroy bacteria *in vivo* are more complex than those concerned with the neutralization of bacterial exotoxins. The vast majority of pathogenic bacteria do not elaborate exotoxins. The products of these bacteria, when injected into man, are quantitatively far less toxic and less specific in their actions than are exotoxins.

In vitro the presence of specific immune bacterial serum plus complement may produce death of certain types of bacteria. When leukocytes are added to this system, many of the bacteria may be found to have been engulfed (phagocytized) by the leukocytes. Somewhat similar mechanisms for bacterial destruction may operate *in vivo*. When virulent bacteria are injected into susceptible animals, there is a progressive diminution in bacteria per unit of blood for the first 6 to 10 hours. This rapid removal of bacteria from the blood is effected partly by circulating polymorphonuclear leukocytes, but largely by the reticuloendothelial tissue. After the initial decline, a secondary increase in number of organisms per unit of blood occurs. If the organism is sufficiently virulent, an overwhelming bacteremia may ensue. It is assumed here that the process of bacterial multiplication is now exceeding the rate

of bacterial destruction. When the same bacteria are injected into an animal previously immunized, the initial clearing mechanism is similar but the secondary increase in bacteria is curtailed and is followed by sterilization of the blood. It would appear that specific antibodies reacting with the bacteria augment the rate of bacterial destruction, which then exceeds the rate of multiplication. In this system it is evident that body tissues play an important role.

One might anticipate that previous immunization of the host with bacteria (killed or attenuated) would lead to control of all types of bacterial infection, but this is certainly not the case. No single explanation for the frequent failure to obtain protection by immunization can be offered. It is reasonable to assume that, in certain types of infection, bacteria become lodged in areas where no antibody is available to render them more susceptible to phagocytosis. Moreover, the virulence of certain bacteria is such that they are capable of destroying the cells which engulf them. Despite the presence of demonstrable antibodies, certain bacteria appear to be able to multiply while within phagocytic cells.

For a long time it has been recognized that patients who recover from certain bacterial infections remain uninfected when exposed subsequently to the same organisms. For example, second infections with *Salmonella typhosa*, *Pasteurella tularensis*, and *Hemophilus pertussis* are quite rare. This constitutes active immunity acquired by natural means. At times the initial disease may have been unrecognized because of its mild or atypical features. It also is known that, with certain other bacterial infections, little or no immunity is afforded by the disease. Examples include repeated episodes of gonococcal urethritis and of bacillary dysentery. Pneumococcal pneumonia and beta-hemolytic streptococcal pharyngitis may leave the host susceptible to second infections. Here it is probable that the host has acquired immunity only to the specific type of the bacterium producing the infection and not to other types of the same bacterium.

Attempts have been made in man to produce active immunity to many infectious agents by injection of killed bacteria or of bacterial products. Most familiar is the immunization to *S. typhosa* and *S. paratyphi* or the immunization of infants to *H. pertussis*. Other vaccines have been used, including those directed to prevent an-

thrax, cholera, plague, bacillary dysentery, tularemia, and pneumococcal pneumonia. In general, immunization with killed bacteria fails to produce the dramatic protection that may be obtained after immunization with toxoids. Frequently, the immunity is relatively slight and the best one can anticipate is a milder form of the disease than in a nonimmunized subject. Also the duration of immunity conferred by vaccines may be short in duration and repeated injections of vaccines at relatively short intervals may be required. Occasionally vaccination is totally unsuccessful. This appears to be true when subjects are immunized to *Brucella abortus*. No protection is conferred in this instance. Recently it has been demonstrated that immunization of man with type-specific polysaccharides of many types of pneumococci has value in preventing infection by these specific types.

Passive transfer of bacterial antibodies by means of immune serums has been used in attempts to treat a variety of diseases. Such immune serums usually are obtained from hyperimmunized animals. Also they are obtained at times from patients convalescing from specific infections. In a few types of infections, good results are obtained. In others only equivocal benefit occurs, while in still others nothing is accomplished. Most effective antibacterial therapy has been accomplished with type-specific antiserums for pneumococcal infections and for infections due to influenzal and meningococcal bacteria. For satisfactory results here, the bacterial antiserum must be given in sufficient quantities, it must contain antibodies that are specific for the individual type of bacterium producing the infection, and it must be administered relatively early in the disease. With any severe bacterial infection, both active proliferation and continual death of organisms are occurring. The accumulated dead bacteria and portions of the bacteria may persist in tissue and in circulating blood for a prolonged period. These substances still retain their antigenicity to a certain extent, and hence can combine with specific antibacterial serum as readily as living bacteria. Quantitative estimations of the amount of antigenic specific pneumococcal polysaccharide that may be present in the lung of a patient at autopsy have demonstrated on several occasions that the amount of antigen present would require many liters of specific antiserum to achieve neutralization.

**VIRAL IMMUNITY.** Certain properties of viruses themselves, and of their selective sites of proliferation in the hosts, lead to problems of immunity that are not encountered in the ordinary bacterial infections. In many respects the behavior of rickettsiae is similar to that of viruses, and they will not, therefore, be considered separately. Viruses are minute agents which pass through filters capable of retaining most bacteria. Unlike most bacteria, viruses can be cultivated only in the presence of living tissue. The amount of virus that may be recovered from tissues of infected man or experimental animals usually is quite small. Many viruses may be grown in tissue cultures or in chick embryos. This permits recovery of much larger quantities of the infectious agent. By suitable chemical and physical technics, a number of viruses now have been obtained in highly purified form. Their physical and chemical characteristics have been examined and many have been photographed with the electron microscope.

Man or animals that have been infected with virus agents usually develop serum antibodies. Such antibodies usually are demonstrable by a neutralization technic in appropriate animals. The method for this procedure and its limitations are considered in a subsequent section (p. 588). In vitro virus antibody may be demonstrated by agglutination, precipitation, and complement fixation. This requires a relatively large quantity of infectious agent and therefore is not always feasible. A few viruses such as mumps and influenza virus have the property of agglutinating erythrocytes such as those of chicken and man in vitro. This agglutination can be prevented by addition of specific antiserum to the virus. This affords a method for detection and approximate quantitation of antibody titers to these viruses.

Unlike most bacteria, viruses tend to reside and proliferate within the body cells of the host. Abundant evidence indicates that the infectious agent within the cells is not affected by the presence of antibodies in surrounding fluid. The virus present in the cell, if it does not kill the cell, may pass into dividing cells and thus remain unexposed to antibody. Certain viruses, however, lead to death of the cell and then upon release may be destroyed or prevented from extension by antibodies present in body fluids. Some viruses appear to reside primarily within surface cells and thus may escape contact with circulating

antibodies. It is necessary to take into consideration these factors in order to account for the frequent instances in which virus infections persist in the host even though neutralizing antibodies to the virus are present in the serum.

Persons who have recovered from many types of specific virus infection are found to be immune to subsequent infection with the same virus agent. For example, second attacks of smallpox, yellow fever, poliomyelitis, and measles are distinctly rare. With a few known virus infections, however, lasting immunity does not result from infection. Multiple attacks of influenza are not uncommon. It has been demonstrated that neutralizing antibodies to influenza virus in the serum may not render the subject immune to subsequent infection with an influenza virus of the same type. Such antibodies may have resulted from previous infection or from immunization with the virus. The susceptibility of such a person to renewed infection might be explained by assuming that the virus proliferating within the cells of the respiratory tract is not in contact with serum antibodies.

In certain virus diseases, active immunity may be conferred by administration of attenuated or killed virus. Most familiar is the vaccination for smallpox with the closely related cowpox virus. Killed or attenuated viruses are employed for vaccination against yellow fever, influenza of the A and B types, and dengue. Progress is being made toward the development of effective vaccines for certain neurotropic viruses. The immunity afforded by these virus vaccines may be slight or marked, and the duration of protection may be quite variable.

As a therapeutic measure, the administration of immune serums to viruses to an affected individual with clinical symptoms has met with little success. It is possible that large amounts of immune serums administered early in the clinical course of measles or mumps may lessen the severity of the disease.

As a prophylactic measure, administration of virus antibodies has been found useful in preventing or at least reducing the likelihood of infections with viruses causing measles, mumps, and infectious hepatitis. The antibody source here may be the whole serum from patients convalescing from specific virus infections. Commonly, however, pooled adult human serum is found to contain specific antibodies to these

viruses, and it has therefore been used for prophylaxis. The use of pooled adult serum carried, however, the risk of transmitting homologous serum jaundice to the recipient. It has been found more satisfactory to employ the gamma-globulin fraction obtained from such serum. The specific antibodies to measles and mumps are concentrated in this fraction, which has been found to be free from contamination with the virus of homologous serum jaundice. In general, gamma-globulin obtained from pooled serum, if administered prophylactically early after exposure to these viruses and prior to the usual onset of symptoms, will modify the disease or prevent it entirely. The greatest benefit has been in the prevention or modification of measles.

The isolation of specific viruses from man during infection may be difficult or impossible. Frequently the diagnosis of these infections is based solely on clinical symptomatology. Most individuals develop specific circulating antibodies to viruses during the course of infection. Such antibodies may not be detected for several weeks after the onset of symptoms, and frequently only during convalescence. Demonstration of a rising titer of circulating antibodies during the convalescent phase, contrasted with the lower titer early in the disease, may permit a specific diagnosis. The technics for demonstrating antibodies to viruses by animal neutralization and more specialized procedures are considered elsewhere (see Chapter 257).

### FINAL CONSIDERATIONS

In this section immunity was considered largely from the standpoint of antigen-antibody interaction. However, it should be emphasized that immunity as it pertains to prevention of infection and to recovery encompasses far more. The problem of natural immunity and of immunity as affected by age, sex, genetic pattern, and environment has not been considered. In many instances factors other than antibodies are dominant in the control of infectious disease.

Considerable progress in our knowledge has occurred during the past three decades. Application of physical and chemical principles has led to the development of purified antibodies and of purified fractions of bacteria and other infectious agents. This, in turn, has enhanced our understanding of immune principles. The development of the quantitative precipitin technic by M.

Heidelberger and co-workers has created the new field of immunochemistry. The applications of this technic to medical and biologic problems are becoming more numerous. Advances have been made in our understanding of haptens. The integration of clinical hypersensitivity reactions with immune principles is just beginning. The continuing search for effective vaccines against bacterial, viral, rickettsial, and even parasitic infections offers promise that in the future many diseases can be prevented by effective immunization.

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## Section 3—Disorders Associated with Reactions to Stress and to Antigenic Substances

# 36

## Survey of Disturbances Related to Mechanisms of Immunity

Paul B. Beeson and Max Michael, Jr.

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### INTRODUCTION

The introduction of certain kinds of foreign matter into the animal body may lead to alterations whereby there is a different reaction to subsequent introduction of the same materials. Phenomena of this type are called immune reactions. Because of common usage the tendency is to regard the mechanisms of immunity as being protective in nature; and of course many of them are. It should be remembered, however, that not all immune reactions are beneficial. There is a fairly large group of diseases, including some common and some very serious entities, in which immune reactions appear to be partly or even wholly responsible for the clinical manifestations. Examples of such diseases will be considered in the present chapter. The terminology in this field is difficult, due to the fact that certain words, such as "allergy" and "hypersensitivity," have been employed with different meanings by various writers. The words "allergy," "hypersensitivity," and "sensi-

tized" will be used here occasionally, but with the intention of implying nothing more than altered reactivity to a foreign substance as a result of previous contact with it.

In the pages to follow various kinds of diseases which may be the result of immune reactions will be considered, beginning with simple examples in which the etiologic role of antigen-antibody reactions is beyond question, and passing on to others in which the evidence is only suggestive.

### ANAPHYLAXIS

Anaphylaxis is an appropriate subject with which to begin a discussion of diseases due to immune mechanisms. Here it is easily demonstrated that an antigen-antibody reaction is the cause of severe, even fatal, symptoms. The antigen which can induce this type of violent reaction may be an inert substance such as egg albumin, which on the first injection has no harmful effect whatever. However, a second injection of the substance, after a suitable time interval, may cause death within a few minutes. The difference lies in the fact that between the first and second injections the host has developed antibodies to the foreign substance, and the reaction between these antibodies and the newly injected antigen causes the symptoms of anaphylaxis. Of the commonly used experimental animals, the guinea pig is especially susceptible to anaphylaxis. One or more weeks after an immunizing injection, this animal may present the following reaction to the reinjection of the same antigen: Within a few seconds he becomes excited, begins to sniff, cough, and wrinkle his nose. He may run about for a short time, but soon stands stiffly and appears to have marked

expiratory dyspnea and cyanosis. He then falls over, may have a convulsion, and dies. The whole complex may take place within a space of five minutes. Autopsy shows the lungs to be distended with air which cannot escape because of intense bronchial muscular spasm. Susceptibility to anaphylaxis can be conferred passively by administration of serum from a sensitized animal of the same or another species.

Much effort has been devoted to an elucidation of the mechanism by which the union of antigen and antibody induces the phenomena of anaphylaxis. The weight of evidence supports the view that the symptoms are caused by the sudden release of histamine or histamine-like substances from various tissues of the body. It is possible that the union of the antigen with antibody so alters the permeability of cell membranes that histamine is released into the circulation. All of the major manifestations of anaphylaxis can be reproduced by the intravenous administration of histamine. The recent finding that anaphylaxis can be prevented by drugs which have the pharmacologic property of antagonism to histamine lends support to this explanation.

There have been several reports of anaphylactic accidents in human beings following the injection of serum or some other antigenic material. Naturally, the clinical data on such accidents are scanty, but the principal symptoms reported are extreme anxiety, dyspnea, cyanosis, cough, unconsciousness, and death. Fortunately, in most cases a fatal outcome can be averted by quick administration of epinephrine. This may be injected subcutaneously, intravenously, or into the heart, but early administration is of the utmost importance. Loss of a few minutes' time in obtaining the epinephrine and the syringe and needle for injecting it may be responsible for the death of the patient.

### THE ARTHUS PHENOMENON

Arthus observed that when an animal was given a series of subcutaneous injections of a non-irritating, but antigenic, substance such as egg albumin or heterologous serum, severe local inflammatory reactions began to appear at the sites of the injections. This, the Arthus phenomenon, is dependent upon the development of specific antibodies to the substance being injected. The inflammatory reaction is due to the local antigen-antibody reaction, with release of

some toxic substance, possibly histamine. Susceptibility to this type of reaction to an antigen can be transferred passively, by administration of specific immune serum.

Clinically, we see examples of the Arthus phenomenon in individuals who receive repeated injections of antigenic material. Severe local reactions may develop during a course of injections of rabies vaccine, which contains brain tissue. The increasingly severe local reactions to scarlet fever toxin, diphtheria toxoid, or typhoid vaccine are of a similar nature. Some of the sterile abscesses which occur in diabetic patients at the sites of insulin injection also belong in this category.

### SERUM SICKNESS

Serum sickness is a disease in which the etiologic role of the immune mechanism is clear. It is of special interest to us here because this disease is used as an example in attempts to explain the pathogenesis of more complex diseases thought to be due to immune reactions.

Serum sickness makes its appearance 5 to 10 days after a therapeutic administration of heterologous serum, as, for example, in the treatment of diphtheria or tetanus. The principal manifestations are fever, urticaria, and arthralgia. These may last from a few hours to several days, and although the patient may appear quite ill for a time, the condition does not cause death. In general, the severity of symptoms is proportional to the amount of serum received; few persons who are given as much as 10 ml. of heterologous serum escape some symptoms of the disease. Persons who have received serum on some previous occasion may develop the symptoms in less time than the usual 5 to 10 days, presumably because antibodies may appear in quantity earlier, in response to a second antigenic stimulus.

There can be no question that the manifestations of serum sickness are related in some way to the reaction between antigen and antibody; the antigen in this case is the foreign serum, and the antibody is that which the patient produces in response to the original injection. This condition differs from anaphylaxis and the Arthus phenomenon in that a second injection of antigen is not needed to produce the disease. At the height of symptoms of serum sickness it is usually possible to show that both the antigen and its antibody are circulating in the blood at

the same time. During the course of the disease the antigen disappears, whereas the amount of antibody increases for several more days.

Here, then, is an illness caused by parenteral administration of a substance which is harmless except for its property of antigenicity. The injection is tolerated without difficulty until specific antibodies are formed in the tissues, and from then until the antigen has been destroyed or eliminated from the body the simultaneous presence of the antigen and its homologous antibody causes the clinical disease, serum sickness.

### INTERGROUP TRANSFUSION REACTIONS

It is well known that a severe reaction is to be expected if erythrocytes containing the A or B agglutinogen are introduced into the blood stream of a person whose blood contains the corresponding isoagglutinin. An individual's blood group is dependent upon the presence or absence of the A and B blood group substances, which are present at birth. The isoagglutinins are not present at birth, but appear sometime during the first year of life. Persons having the A agglutinogen develop  $\beta$  agglutinins, while those with the B agglutinogen develop  $\alpha$  agglutinins. Individuals who belong to Group O—that is, those who have neither A nor B agglutinogen—develop both agglutinins; whereas those having both the A and B substances develop neither agglutinin. This suggests that all of us are subject to antigenic stimuli capable of provoking either the  $\alpha$  or the  $\beta$  agglutinin, but that each person's response is determined by the blood group which he inherits. It is, of course, a fundamental rule of immunology that antibodies cannot be developed against substances normally present in the host's circulation. Conceivably, the antigenic stimuli which call forth the formation of the  $\alpha$  and  $\beta$  agglutinins are in the various bacteria which normally parasitize the body. We know, for example, that the Forssman antigen, present in many bacteria, contains a substance immunologically similar to the blood group A substance.

In an incompatible transfusion the isoagglutinins react with the donor's red blood corpuscles, causing intravascular agglutination and lysis. The hemoglobin liberated in the circulating blood is removed by the kidneys and excreted in the urine. The danger of this type of accident lies in the damage which may be sustained by the

kidneys. There may be extensive tubular injury, with oliguria or anuria; and death may ensue from acute renal failure.

### RH FACTOR—ERYTHROBLASTOSIS FOETALIS: INTRAGROUP TRANSFUSION REACTIONS

There is present in the erythrocytes of 85 per cent of the white population an antigenic fraction—the Rh factor; its inheritance is independent of the A and B agglutinogens. The Rh factor is important in clinical medicine because it figures in the pathogenesis of erythroblastosis foetalis, and also in certain intragroup transfusion reactions.

**Erythroblastosis Foetalis.** A mother whose erythrocytes do not contain the Rh antigen (i.e., Rh negative), and a father whose erythrocytes do contain the Rh antigen (i.e., Rh positive), may have a child that is Rh positive. During the period of gestation, Rh antigenic components of the fetus may pass across the placental barrier and enter the maternal circulation. This is an antigen foreign to the mother and calls forth the production of anti-Rh antibodies. These antibodies may then pass back across the placental barrier and react with the fetal red cells, producing the syndrome of erythroblastosis foetalis.

**Intragroup Transfusion Reactions.** If an Rh negative person receives a transfusion from an Rh positive donor, he may develop anti-Rh antibodies. There will not be a reaction to the first transfusion, but in subsequent transfusions with Rh positive blood he may have a hemolytic reaction caused by the union of his anti-Rh antibodies with the donor cells. This reaction is, of course, independent of the patient's A-B grouping, and is called an intragroup reaction. Mothers of Rh positive infants are also subject to this type of reaction because of the Rh antibodies previously induced in them by the fetal antigen.

### ASTHMA, HAY FEVER, URTICARIA, FOOD ALLERGY

It is well known, even to laymen, that some persons develop symptoms from contact with substances which are quite harmless to most individuals. These are commonly referred to as allergic manifestations. They may take different forms, such as lacrimation and coryza (hay fever), severe dyspnea with wheezing (asthma),

itching eruption of the skin (urticaria), or abdominal pain (food allergy). The substance responsible may be a pollen, a food, dust, or the dander of an animal. In many instances it is possible to identify the offending agent, and to show by one or another means that the person has developed antibodies to it. Skin tests with one of these materials may give rise to reactions of the immediate, or anaphylactic, type. The clinical manifestations in these conditions appear to be caused by liberation of histamine in one of the "shock" organs (skin, respiratory tract, or gastrointestinal tract), producing an exudative type of inflammatory reaction. In many instances the "shock" organ seems to be selected because it is the one which ordinarily comes into contact with the antigen, as, for example, the coryza of hay fever. In other cases, however, the "shock" organ is not the portal of entry, as in the urticaria or asthma which may occur after the ingestion of a certain food.

It should be pointed out that all cases of bronchial asthma, urticaria, and suspected food allergy do not conform to the foregoing simplified concept. Even after the most elaborate studies there may be no evidence that the symptoms result from contact with some external agent. In such cases the pathogenesis may be considerably more complex; nevertheless, it probably involves reactions of immunity.

For many years it has been known that some of these conditions, especially hay fever, can be ameliorated by a course of parenteral injections of the specific antigen. The reason for this beneficial effect was difficult to explain, but was sometimes spoken of as "desensitization." The findings of Loveless and others point, however, to a more persuasive explanation—namely, that two kinds of antibodies may be produced in response to an antigen. One type, the so-called "sensitizing" antibody, causes symptoms of the disease when it unites with its corresponding antigen. The other type, the "blocking" antibody, unites with the antigen without causing symptoms, but thereby prevents union of the antigen with sensitizing antibody. It may be, then, that the benefit sometimes resulting from a course of antigen injections is due to formation of blocking antibodies.

#### REACTIONS TO DRUGS

It has been known for a long time that some people exhibit peculiar reactions, or idiosyn-

crasies, to certain drugs: reactions which differ from the usual toxic effects of the drugs. It is now generally believed that many of these idiosyncrasies are the result of immune reactions. That this was not recognized earlier is due to the fact that the compounds which may induce such reactions are often simple chemical structures which cannot act as antigens. It was shown by Landsteiner and others, however, that simple chemical compounds can participate in antigen-antibody reactions if linked with large molecules. Such a linkage between a drug and a body protein may occur after ingestion. The drug then serves as a hapten, determining the immunologic specificity of the antigen.

Immune reactions to drugs may have various manifestations, the commonest being skin eruptions and fever. More serious are granulocytopenia, purpura, or acute hemolytic anemia. The time of onset of symptoms is variable, but it is most often during the second week of therapy; that is, about the time antibodies would be expected to appear. Among the agents which most frequently produce this type of reaction are the sulfonamides, thiouracil compounds, and penicillin. Reactions to penicillin treatment are encountered fairly often at present, and they show a striking resemblance to serum sickness: urticaria, arthralgia, and fever. Another interesting drug reaction which resembles serum sickness is that which may develop during the second week of treatment with an arsenical; this has been termed "erythema of the ninth day."

#### ID REACTIONS

The name "id" has been applied to certain secondary skin eruptions which occur at a distance from an area of skin infection. When the etiologic agent of the primary lesion is known, the secondary lesion is designated by adding the term "id" as a suffix—e.g., tuberculid. Lesions of this type have received considerable study, and the prevailing concept of their pathogenesis is that they represent immune reactions to the infecting agent or to an antigenic fraction of it. Presumably, the antigenic material is carried to the distant skin area in the blood stream and the eruption there is the result of a local immune reaction to it. Proof of this concept is difficult, because the etiologic agent can seldom be demonstrated at the secondary focus. The best evidence in support of it is the fact that treatment of the

primary infected area, if effective, usually causes the "id" to disappear.

The commonest "id" reaction is that which is associated with trichophyton infection of the feet (trichophytid). This is usually manifested by a vesicular eruption on the hands. "Ids" are also observed in other fungous infections of the skin and in syphilis. The generalized eruption of lymphogranuloma venereum has similar characteristics; in fact, it would seem that the id phenomenon occurs almost exclusively in association with those infections which cause the tuberculin type of skin sensitivity.

### CONTACT DERMATITIS

The skin, especially the outer layers of the epidermis, may become sensitized by contact with a particular agent, which in itself is not usually harmful. Repeated contact with such a substance may lead to the development of a dermatitis characterized by erythema and vesication. Many different materials have been found to be capable of causing this type of reaction. The site of the dermatitis depends upon the nature of the contact with the offending agent. An eruption about the eyelids suggests eye make-up as the cause; around the wrist, a watch band; on the leg, some substance in the stocking; on the hands, something encountered in one's occupation—e.g., a soap or chemical. Sensitization of one area of the skin may result in a similar change over the entire surface. In other cases, however, only the area of contact may be affected.

Antibodies are rarely demonstrable in cases of contact dermatitis. Nevertheless, there can be little question that this condition belongs in the category of hypersensitive states. Investigations on the subject of poison ivy dermatitis have helped in our understanding of the problem. It has been shown that the application of poison ivy extract to the skin of a normal infant produces no harmful reaction, but that a subsequent application, after a week or two, will irritate to the point of vesication. The majority of adults react to such an extract with vesication, presumably because they have been sensitized by previous contact with the plant. Other evidences that immune mechanisms participate in the pathogenesis of contact dermatitis are: (1) The skin sensitivity is specific for a particular agent. (2) There is always an incubation period from

the time of first contact until the development of dermatitis, which averages 6 to 10 days, but may be much longer. (3) A period of time, 12 to 48 hours, is required for the reaction to become manifest, even after the skin has become sensitized.

### NEUROLOGIC COMPLICATIONS FROM INJECTION OF BRAIN TISSUE VACCINE

There have been numerous instances of acute neurologic disorders resulting from parenteral injection of vaccines containing nerve tissue. Vaccines of this kind have been employed in prophylaxis against rabies and yellow fever, and in the diagnosis of lymphogranuloma venereum (Frei antigen). The clinical manifestations of these neurologic complications are variable, the commonest picture being that of a low-grade encephalomyelitis. Symptoms usually develop about 10 to 20 days after the first injection of the vaccine. Several theories have been offered regarding the cause of these reactions. One which appears to be acceptable is that the person develops antibrain antibodies in response to the injections of heterologous brain tissue. Such antibodies then cross react with his own nerve tissue, producing inflammation and disease. It seems significant in this connection that the incidence of neurologic complications is higher among persons receiving second or third courses of rabies immunization than in persons receiving first courses. Further evidence has been obtained in animals, where severe brain damage has been produced by injecting heterologous and even homologous brain tissue; antibrain antibodies have been demonstrated in the serums of such animals.

### PHYSICAL "ALLERGY"

There are individuals who, on exposure to heat, cold, or sunlight, have symptoms resembling those of hypersensitivity reactions. There may be urticaria, angioneurotic edema, joint pains, fever, or vasomotor rhinitis. The reactions may be confined to the part exposed, or may be generalized.

It seems likely that in many instances physical "allergy" is nothing more than an unusual susceptibility to injury by the particular physical agent, with the consequent liberation of excessive amounts of histamine or histamine-like substances. Attempts to produce physical "al-

lergies" in experimental animals have seldom met with success. There are, however, some well-documented reports of cases in human beings where sensitivity to physical agents has been transferred passively from the patient to a normal individual, by means of the P-K reaction (see p. 444). In such instances it appears that an immune reaction is responsible for the clinical manifestations.

### LOEFFLER'S SYNDROME

Loeffler, in 1929, described a syndrome of transient pulmonary infiltrations, eosinophilia, and few or no clinical symptoms. It appears that several conditions are capable of inciting the syndrome. Among them are: infestation with the parasites *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis*, *Fasciola hepatica*, *Trichinella spiralis*; infection due to *Coccidioides immitis*; contact with the privet flower; and sulfonamide sensitization. Transient pulmonary infiltration and eosinophilia, consistent with Loeffler's syndrome, have also been observed in patients subject to bronchial asthma.

Because of the benign nature of the disease, there have been few opportunities to study its pathology. The pulmonary lesions in four patients whose deaths were accidental were found to consist of bronchitis or bronchiolitis or pneumonia, with eosinophils in the exudate and in alveolar septums. In those patients with bronchial asthma and Loeffler's syndrome, the striking findings were vascular changes varying from intimal thickening of the small arteries to necrotizing arteritis with perivascular eosinophilia.

The syndrome has been produced experimentally by the intratracheal instillation of horse serum in rabbits previously injected with the serum. In this experimentally induced disease there were eosinophils in the tracheal and bronchial mucosa. In the lungs, congestion, edema, atelectasis, emphysema, and an eosinophilic pneumonia were noted. This evidence suggests that Loeffler's syndrome may be due to an immune reaction which takes place principally in the lungs.

### GLOMERULONEPHRITIS AND RHEUMATIC FEVER

It is convenient to consider glomerulonephritis and rheumatic fever together, since they have certain common features in their pathogene-

sis. Both diseases appear to be complications of hemolytic streptococcal infection. This relationship is established, not only by clinical observations and cultural studies, but also by serologic tests. Nearly all patients with acute rheumatic fever or glomerulonephritis give a history suggestive of a preceding streptococcal infection and have elevated streptococcal antibody titer in the blood. Despite the constant association with streptococcal infection, the manifestations of these diseases do not appear to be those of simple infectious processes. First of all, there is always a latent period of many days between the beginning of the streptococcal infection and the onset of symptoms of either disease. Second, it is not possible to demonstrate hemolytic streptococci in the affected tissues, whether they be kidney, heart, or joint. Third, chemotherapeutic agents such as the sulfonamides and penicillin, which are highly effective in the treatment of acute streptococcal infections, have no curative effect whatever in glomerulonephritis and rheumatic fever. It is generally believed that these late complications are due to some type of immune response to the streptococcal infection. This could be either in the form of an abnormal response to the streptococcus, or some process whereby the person's own tissues are so changed by the streptococcal infection that they become antigenic. The antibodies evoked by such antigens could then react with the corresponding normal tissues, producing manifestations of nephritis or rheumatic fever.

The development and course of these two diseases show similarities to serum sickness, in which participation of an immune mechanism is obvious. Following the initial streptococcal infection, the symptoms of rheumatic fever and glomerulonephritis develop only after a latent period of two or three weeks. This resembles the interval that occurs between the administration of serum and the onset of symptoms of serum sickness. Indeed, some of the clinical features of serum sickness are observed in rheumatic fever and glomerulonephritis. The joint pains, urticaria, and occasional disturbances of conduction in the heart are like the joint pains, skin lesions, and conduction abnormalities of rheumatic fever. Similarly, oliguria, proteinuria, cylindruria, and the chloride, water, and nitrogen retention observed in serum sickness are seen in acute glomerulonephritis.

When a reinfection with the streptococcus precipitates an exacerbation of glomerulonephritis, the latent period may be shortened to two or three days, just as the development of serum sickness is accelerated in a previously sensitized individual. A shortening of the latent period between streptococcal infection and recurrent rheumatic fever is not obvious, although recent careful studies by Rantz, Boisvert, and Spink showed that, despite the apparent long latent interval, signs consistent with low-grade rheumatic fever begin to develop shortly after the symptoms of the streptococcal infection. This may mean that previous sensitization had occurred. Moreover, the fact that rheumatic fever and glomerulonephritis are rarely encountered in children under three, suggests the possibility that previous streptococcal infection may have to occur before an individual becomes susceptible to these complications.

The pathologic findings in patients dying at various stages of streptococcal infection have demonstrated interstitial lymphocytic infiltrates in the heart and kidney comparable to the findings resulting from an antigen-antibody reaction. Rich found that rabbits which were given injections of horse serum developed lesions in the heart muscle resembling Aschoff bodies, as well as diffuse valvulitis, focal collagen swelling, and degeneration similar to the changes in rheumatic fever.

It has been suggested by many writers that the pathogenesis of rheumatic fever and glomerulonephritis involves the development of organ-specific antibodies. It is possible, for example, to produce a disease similar to glomerulonephritis in experimental animals by injection of antikidney serum. Some workers have reported the finding of antikidney antibodies in the serums of patients convalescent from hemolytic streptococcal infection, while others have claimed that antibodies to heart muscle can be demonstrated in the serums of patients with acute rheumatic fever. It is difficult to assess the significance of such evidence.

To recapitulate, there is a considerable body of evidence which supports the concept that rheumatic fever and glomerulonephritis are caused by an abnormal immune response to a streptococcal infection. This may be due to a reaction in certain organs to products of the streptococcus. Or it may be due to alteration of the host's tissues by

the streptococcal infection in such a way that these become capable of acting as antigens. Organ-specific antibodies are then produced by the host, and the resulting antigen-antibody reaction causes the manifestations of the disease.

### ERYTHEMA NODOSUM

Erythema nodosum is a syndrome characterized by fever, malaise, and painful erythematous areas on the skin of the extremities. Frequently, there is acute polyarthritis, and in many cases x-ray of the chest shows enlargement of the hilar lymph nodes. Symptoms may persist from a few days to a few weeks. This condition sometimes presents itself as an isolated entity unrelated to any other disease. More frequently, however, it occurs in association with some other condition. The most frequent of these are hemolytic streptococcal infections and early pulmonary tuberculosis. Other conditions with which erythema nodosum may be associated are coccidioidomycosis, lymphogranuloma venereum, trichophytosis, and sensitivity reactions to such drugs as sulfonamides, bromides, and iodides. It will be observed that all of these conditions have been considered previously in this chapter as entities in which immune mechanisms appear to play a prominent part. Furthermore, the appearance of erythema nodosum occasionally seems to result from an immunologic diagnostic procedure such as a tuberculin or Frei test. Because of this evidence and the failure of all efforts to demonstrate any other etiologic mechanism, the prevailing opinion is that erythema nodosum is a nonspecific syndrome caused by an immune response to an infection or drug.

### PERIARTERITIS NODOSA

The high incidence of bronchial asthma and the blood and tissue eosinophilia often noted in patients with periarteritis nodosa have led many physicians to suggest that hypersensitivity plays a part in its pathogenesis. Rich's recent observations have established this hypothesis on a firmer basis. He found histologic evidence of periarteritis nodosa in tissues of patients suffering sensitivity reactions to horse serum and certain drugs. Moreover, he succeeded in producing characteristic pathologic lesions of periarteritis nodosa in rabbits by giving them injections of horse serum or other foreign protein. He has suggested that the lesions of periarteritis nodosa may begin as

"urticarial wheals" in the arterial walls, with resulting local necrosis and inflammatory changes. Rich's findings have been confirmed and extended by Hawn and Janeway, using purified protein fractions from bovine plasma. They found that arterial lesions were produced readily with the albumin fraction, whereas lesions resembling those of glomerulonephritis resulted from an injection of the globulin fraction.

Among the substances that have appeared to precipitate periarteritis nodosa in human beings are horse serum, sulfonamides, iodides, and thio-uracil. It is possible that careful studies of other patients with periarteritis nodosa will reveal more substances capable of initiating this disease.

It should be pointed out, on the other hand, that lesions resembling those of periarteritis nodosa have been produced in experimental animals by various procedures which lead to the development of arterial hypertension, such as injections of adrenal cortical hormone and interference with the blood supply of the kidneys. It is not easy to incriminate hypersensitivity in the pathogenesis of this form of periarteritis nodosa.

#### IMMUNE MECHANISMS IN BACTERIAL INFECTIONS

Some of the damage produced by bacterial parasitism may be the result of the host's immune response to the foreign agent. The best example of this is seen in tuberculosis. The tubercle bacillus is itself almost devoid of demonstrable toxicity. When it first gains entrance to the body there is only a slight inflammatory reaction, hardly more than that which is provoked by any bland foreign material. After about two weeks, however, the situation becomes quite different. The bacterial cells now seem to act like powerful irritants, exciting severe reactions in the tissues. This phenomenon was first observed by Koch; and the series of events which he described in the guinea pig is referred to as the "Koch phenomenon." He noted that when he injected tubercle bacilli into the subcutaneous tissues of the guinea pig there was little or no visible reaction for 10 to 14 days. During that period the bacteria were transported to the regional lymph nodes. At the end of 10 to 14 days the site of injection took on the appearance of an inflammatory reaction, and subsequently there was necrosis and sloughing. When the same animal was later subjected to another inoculation of bacteria, the course was very

different. Within one or two days the site of inoculation became acutely inflamed, and this reaction quickly progressed to necrosis and sloughing. There was, furthermore, no evidence of spread of the infection to the regional lymph nodes of the rest of the body, the immune reaction apparently serving to prevent dissemination of the infection. Koch found that this alteration in response could be elicited not only by living but also by killed tubercle bacilli, or by extracts of culture medium in which they had grown.

The different forms of pulmonary tuberculosis seen in man show a similarity to the "Koch phenomenon" in the guinea pig. The primary pulmonary infection is usually characterized by an indolent focus in the parenchyma of the lung which rarely causes cavitation but which is associated with extensive invasion of the hilar lymph nodes. The reinfection type of pulmonary tuberculosis, on the other hand, is characterized by a marked local inflammatory reaction in the lung which often causes breakdown of tissues (cavitation), and there is little or no tendency to spread to the regional lymph nodes.

We take advantage of the immune reactions to products of the tubercle bacillus in the diagnostic skin test for tuberculosis—the tuberculin test. Persons previously infected with the tubercle bacillus show a skin reaction consisting of erythema and induration following the injection of a small quantity of the tubercle bacillus protein (O.T. or P.P.D.). In some individuals the sensitivity is so marked that an inflammatory reaction can be observed in response to as little as .00001 mg. of Old Tuberculin. Yet a person who has never previously had contact with the organism shows no reaction even to large quantities of this material. A spectacular demonstration of this was reported by a German physician, who injected 20 Gm. of O.T. into a young infant, reportedly without ill effect.

Many of the mycotic infections have clinical features which resemble those of tuberculosis, and there is reason to believe that their manifestations, too, may be largely those of the immune response of the individual. It is interesting to note, for example, that actinomycosis can seldom be produced in an experimental animal with a single injection of actinomyces. Only by repeated injections can a state be induced whereby disease follows injection of this agent. Many writers have suggested that some of the late

manifestations of syphilis are due in part to immune mechanisms.

Subacute bacterial endocarditis has features which suggest that immune mechanisms play a part in its manifestations. The causative bacteria usually have little or no ability to produce disease elsewhere in the body. Furthermore, patients with bacterial endocarditis usually show high titers of circulating antibodies for the offending mechanism. In experimental animals the disease can be produced by repeated injections of live organisms, but very rarely can it be produced by a single inoculation. Horses are naturally resistant to pneumococcal infection and are inoculated with live cultures; yet in the manufacture of antipneumococcal horse serum it has been observed that the animals occasionally develop pneumococcal endocarditis due to the very organisms for which they have a high titer of circulating antibodies. It is conceivable, then, that this peculiar disease may be due in part to the reactions of immunity; possibly the intravascular clumping of bacteria favors their lodgement on a damaged heart valve.

### SHWARTZMAN PHENOMENON

A peculiar kind of immune phenomenon was demonstrated by Shwartzman in rabbits. He observed a purpuric reaction in the skin caused by the intravenous administration of the endotoxins of certain bacteria. The reaction appeared only at the site of a previous intradermal injection of the same material. Histologic examination of this area showed severe capillary damage, with hemorrhage. The bacterial fraction responsible for this reaction has been demonstrated in at least one case (*Serratia marcescens*) to be a carbohydrate, and to be the same as the "pyrogen" fraction, which causes elevation of body temperature. Gram-negative bacteria, especially bacillary forms such as *Escherichia coli* and *Salmonella typhosa*, are particularly rich in the Shwartzman toxin.

There are several remarkable features about the Shwartzman phenomenon. The purpuric reaction can be elicited only when the intravenous inoculation follows the intradermal inoculation by approximately 24 hours. A second intradermal injection of the same area will not cause purpura; apparently the provocative dose must be delivered via the blood stream. Toxic fractions from the two different bacterial species not anti-

genically related can be employed, one for the preparatory intradermal, and one for the provocative intravenous, dose. Yet, on the other hand, the reaction can be modified by specific antibodies, in that animals can be protected against it by active or passive immunization against the toxin used as the provocative agent. The exact mechanism of the Shwartzman phenomenon has not been elucidated.

From time to time it has been suggested that various human diseases are examples of the Shwartzman type of reaction. For example, the hemorrhagic rashes seen in certain fulminating infections, especially meningococcemia, could be examples of the Shwartzman phenomenon. It is conceivable that, in the course of an illness characterized by repeated bacterial invasion of the blood stream, bacteria or their products may lodge in certain locations, especially the skin, and "prepare" them, just as is done in the laboratory animal by the intradermal inoculation of toxin. Many hours later another invasion of the blood stream could deliver the same bacterial toxin to the "prepared" site, and cause the hemorrhagic reaction. Another clinical condition which could be due to a Shwartzman reaction is acute hemorrhagic pancreatitis. Certain types of fulminating lung abscesses associated with acute suppuration in the pharynx may belong in this category. Some experiments have been reported in which focal hemorrhagic reactions, resembling the Shwartzman reaction, have been produced in tuberculous lesions by the intravenous injection of various bacteria. It may be that this is the basis of the clinical observation that intercurrent infection may cause a flare-up of a tuberculous lesion. It should be emphasized, however, that in none of the examples given is the evidence for a Shwartzman type of mechanism conclusive.

### DIAGNOSTIC PROCEDURES

In many of the syndromes under discussion the etiologic role of an antigen-antibody reaction seems firmly established. In others, the evidence is only suggestive. It is often possible, however, by the use of suitable tests, to demonstrate that antibody to a given agent is present in the serum, or that a hypersensitive state exists in some tissue. Diagnostic tests, whether carried out in vitro or in vivo, depend upon the union of antigen and antibody.

**Skin Tests.** A small amount of the antigen to be tested is injected intracutaneously, usually on the flexor surface of the forearm. Two types of reaction may be seen: the immediate, and the delayed, or tuberculin, type of reaction. The *immediate* type of skin reaction is found in individuals sensitive to inanimate objects such as horse serum, pollens, dust, or animal integument. It is characterized by a wheal surrounded by erythema, which appears within 10 to 20 minutes, and persists for only a few minutes. The reaction is thought to be caused by liberation of histamine at the site of the antigen-antibody union. This alters capillary permeability, allowing plasma to escape into the tissue and form a wheal. Occasionally, the antigen used in the skin test also provokes a general reaction such as asthma. The *delayed*, or *tuberculin*, type of skin reaction is seen in individuals sensitive to living parasites, such as the tubercle bacillus, viruses, and fungi. It becomes visible in 24 to 48 hours, and may persist for several days. The reaction consists of erythema and palpable induration; occasionally it is so intense that there is necrosis of the skin. The mechanism of this type of skin reaction is not clearly understood; however, Chase's demonstration that tuberculin sensitivity can be transferred passively indicates that it too depends on the union of antigen with a humoral substance.

**Passive Transfer Tests.** In some patients the only method by which circulating antibodies can be demonstrated is through use of the Prausnitz-Küstner (P-K) reaction. The serum to be tested is injected, intracutaneously, in a normal subject. Twenty-four hours later the suspected antigen is injected into the prepared site and also into another area. A positive reaction consists of an immediate type of reaction in the prepared site, but not in the control area. The P-K reaction is useful in children and also in others with such widespread dermatitis that little normal skin is available for testing. Of more fundamental significance is the fact that it provides positive evidence of humoral antibodies in some cases where in vitro tests are negative.

**Patch Tests.** These are used principally in investigation of the etiology of contact dermatitis. A small amount of the suspected agent is applied to the skin and held there by tape or bandage for 24 to 48 hours. A positive reaction is indicated by erythema and vesicles at the site of contact. It

must be remembered that in some types of contact dermatitis only a limited area of skin is sensitized; that patch tests elsewhere will be negative.

**Test Dose Methods.** In some cases the only method of demonstrating the hypersensitive nature of a symptom complex is to expose the patient to further contact with the material in question. This measure is employed principally in determining whether a patient is sensitive to a certain drug. A small dose of the drug is given, and the patient is then observed carefully for fever, skin eruption, or change in blood picture.

**Elimination Diets.** When some article of food is suspected as the causative agent in a disease, the use of an "elimination diet" may serve to identify the offending food. The one which is suspected—e.g., milk, chocolate, or coffee—is omitted from the diet for several days. If the symptoms subside during the period of omission and recur when the food is again added to the diet, strong evidence of a cause-and-effect relationship has been furnished. When no ground exists for suspecting any particular food, the patient can be given a diet consisting of a few foods which rarely cause allergy, such as pears, rice, and lamb. Then other foods are added to the diet one at a time until symptoms recur.

**In Vitro Methods.** These are often technically more difficult than the procedures just described but may be more accurate and safer, and give more quantitative data. Antibodies may be demonstrable in the patient's serum by means of precipitin, agglutination, or complement-fixation tests. The choice of method must be made according to the individual situation, but the precipitin method is the one most commonly employed. There are numerous instances where antibodies seem to be present in the serum (as evidenced, for example, by a positive P-K reaction), yet where in vitro tests are negative. Undoubtedly our in vitro methods are not sufficiently sensitive to detect small quantities of antibody.

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## 37

### Allergic Disorders

Harry L. Alexander

#### Introduction

##### Atopy

- Bronchial Asthma
- Hay Fever
- Vasomotor Rhinitis
- Gastrointestinal Atopy
- Headaches
- Dermatoses
- Other Atopic Disorders
- Serum Sickness
- Bacterial Allergy
- Allergy to Drugs
- Vascular Allergy

#### INTRODUCTION

As indicated in the chapter on diseases due to immune mechanisms, the term "allergy," as originally used, implied an altered tissue reactivity as a result of repeated contact with foreign substances such as bacteria or serums. The pathologic and immunologic aspects of this phenomenon were subjects of intensive study for years before its broad clinical applications were appreciated. About 1915, bronchial asthma, hay fever, urticaria, and eczema (later called the atopic group) were found to be expressions of hypersensitivity to foreign substances. Inasmuch as these disorders resulted from an allergic reaction, the term "allergy" was applied to them, and since then its usage in clinical medicine has implied a group of diseases rather than its broader meaning of altered tissue reactions. To the atopic disorders were added serum sickness, certain infectious diseases, contact dermatitis,

hypersensitivity to drugs and, recently, some instances of periarthritis nodosa, because in each it was shown that symptoms could be produced by repeated contact with substances foreign to the body. The mechanism that produces each of these apparently differs one from another, as well as do tissue changes which give rise to symptoms. The failure to appreciate the fact that symptoms as well as lesions of allergy may be mediated by several underlying processes, has led to clinical confusion.

Our knowledge of the differentiation of various types of allergy is due largely to pathologists who have adhered to the original meaning of its definition. They not only have observed the altered tissue reactions in the several forms of human hypersensitivity, but also have provided clues which would link them together. These provocative ideas have done much to lift allergy out of a restricted specialized area and integrate it with broader aspects of medicine. Its substantial participation in the fields of pathology, immunology, internal medicine, dermatology, and other subspecialties has long been known, but until recently each has been dealt with separately. In this chapter, in keeping with the present trend of thought, allergy will be considered as a clinical entity with its parts integrated by known facts or suggestive implications.

With one or two exceptions to be noted, al-

Table 39  
CLINICAL EXPRESSIONS OF HUMAN HYPERSENSITIVENESS

Type	Antibody	Principal Clinical Manifestations
Atopy.....	Reagin	Bronchial asthma, hay fever, vasomotor rhinitis, acute urticaria
"Atopic-like" (intrinsic) syndromes.....	Not demonstrated	Bronchial asthma, vasomotor rhinitis, chronic urticaria
Serum sickness.....	Precipitin	Fever, urticaria (purpura), arthralgia
Bacterial allergy.....	Not isolated	Symptoms of disease involved
Allergy to drugs.....	Not isolated	Skin eruptions, fever, arthralgia, various visceral manifestations
Contact dermatitis.....	Not isolated	Eczema
Vascular allergy.....	..	Symptoms of periarteritis nodosa

lergic reactions are immunologic processes and occur as a result of contact with a foreign substance (allergen) with a specific antibody to it. This antibody is induced by repeated exposure to the allergen, and resides in tissue cells. In some instances the antibody appears also in the blood stream and may be measured; in others it is firmly attached to tissue cells and can be demonstrated; and in some its presence is implied.

In table 39, the various clinical expressions of allergy are given. There is apparently no common allergen or antibody or clinical manifestation that links these together. However, when the pathology of each is compared, their relationship to one broad underlying process will suggest itself.

### ATOPY

Some 35 years ago, bronchial asthma, hay fever, and other members of the atopic group were considered separate diseases although vaguely related. The revelation that all were expressions of allergy was a decided advance in clinical medicine. Its practical value was at once apparent, for the introduction of this new conception was accompanied by a skin test which promised to reveal the foreign substance responsible for symptoms. Although the term "allergy" came to be used clinically to indicate this group of cases, "atopy" (strange disease) was employed later.

Atopy differs from other forms of allergy in three respects. First, it is the only one that is transmitted by heredity and according to Mendelian law; all other types are acquired. This is an important clinical consideration in differential diagnosis, for bronchial asthma may simu-

late bronchitis, and vasomotor rhinitis, the common cold. A history of asthma or hay fever in the immediate family would greatly favor the probability of allergy. One is born not with symptoms of atopy but with the capacity to become hypersensitive (to develop antibodies) after repeated contact with an allergen.

Second, in atopy, allergens are nontoxic substances such as pollens and foods which induce an antibody, "atopic reagin," sometimes called the "skin-sensitizing antibody" because it is frequently deposited in cutaneous tissue. When present there in large amounts, it enters the blood stream, and can be demonstrated by the passive transfer test previously described (p. 444). This test, as will be shown, has definite diagnostic value. Atopic reagin differs from other allergic antibodies particularly in its lability to heat. Another antibody, the so-called "blocking" antibody, appears in patients with hay fever after treatment with pollen antigen. Whether or not the two are separable or are different expressions of one antibody, depends on the validity of the "unitarian hypothesis."

Third, the primary lesion of atopy is edema. This appears in the nasal mucosa as hay fever and vasomotor rhinitis. It contributes to bronchial asthma and is responsible for urticarial wheals. In bronchial asthma and gastrointestinal allergy, smooth-muscle constriction and increased secretion from mucous glands occur also. The edema appears almost immediately on contact between an allergen and its specific antibody. This is demonstrated readily by a positive skin reaction in which the edema in the form of a wheal develops within a few minutes after an allergen has been applied to the skin of an indi-

vidual hypersensitive to it. The prevailing theory that accounts for edema presumes that histamine, or something akin to it (H-substance), is released from tissue cells on contact between an allergen and its specific antibody. Three facts among others tend to support this theory. One is that histamine may cause a wheal structurally the same as an allergic one and within the same time when both are laid down simultaneously. The second is the demonstration that an anti-histamine drug, as "Benadryl," taken previous to testing, will prevent both histamine and allergic skin reactions. Third, increased histamine in the blood has been found during induced anaphylactic shock in guinea pigs in which symptoms of this form of hypersensitiveness closely resemble those of bronchial asthma, although this phenomenon is absent in other animals with anaphylaxis. Despite these and other suggestive indications that histamine is responsible for atopic lesions, this theory is considered by some authorities as far from proved.

The release of histamine apparently has a precursor mechanism which is not understood. It evidently involves acetylcholine and the enzyme systems of each. The participation of acetylcholine in atopy is important, for vagal stimulation which presumably releases it will produce atopic lesions, as smooth-muscle spasm and increased mucous secretions, and it contributes to edema by vascular dilatation. This explains why epinephrine, which causes sympathetic stimulation and counteracts cholinergic action, is so effective on atopic lesions.

There are three atopic manifestations—namely, bronchial asthma, vasomotor rhinitis, and chronic urticaria—wherein no antibody can be demonstrated in many instances. Not only can no skin reaction be demonstrated, but also there is no response to methods of environmental control, wherein common allergens are excluded.

The recognition that bronchial asthma or urticaria may not be allergic and yet may have identical signs and symptoms of the atopic types, has been an important advance. It has explained the previous failures of treatment of these cases which are referred to as "intrinsic," or "nonatopic," asthma or urticaria, since no extrinsic allergen is apparent. Their etiology is unknown but it is believed that it is due to release of histamine by the tissues involved without the mediation of an antigen-antibody mecha-

nism. It has been demonstrated that excessive amounts of histamine appear in the blood stream in a variety of pathologic conditions, as certain infections, the alarm reaction, peptone shock, etc., and apparently it is responsible for whealing when dermatographic skin is stroked. This theory remains unsupported by factual data. The distinction between atopic and nonatopic asthma, vasomotor rhinitis and urticaria, however, has much clinical importance, for as a rule the latter is the more severe and, because no antiallergic treatment is available, is the more intractable. Although both types have identical points of similarity, there are distinctions by which they may be separated. These appear in table 40.

Perhaps the most suggestive distinction is the age of onset. The majority of atopic individuals (those who have the capacity to develop antibodies against extrinsic allergens) do so before the age of twenty. Moreover, the later in life symptoms first appear in atopic individuals, the milder they are apt to be. With nonatopic manifestations the opposite is true. They usually appear after the age of thirty, and more commonly in the forties or later. Given a patient who, at the age of forty, develops bronchial asthma which soon becomes severe with attacks of status asthmaticus, or urticaria which is intense and resists antiallergic treatment, there is a far greater probability that these are nonatopic rather than allergic. On the other hand, a child who becomes subject to asthma at the age of five almost surely is hypersensitive to a specific allergen which it inhales or ingests.

The separation of these two groups is not always simple, for an atopic asthmatic occasionally may develop symptoms later in life or may lose his hypersensitiveness and develop characteristics of the nonatopic group, and a nonatopic patient occasionally may produce a positive skin test.

In both atopic and nonatopic types of disorders, there is an eosinophilia. This originates in the bone marrow and appears in the blood stream as eosinophils are transported to the tissues involved, where they are found in large numbers. The function of these cells in allergy is unknown. There is suggestive evidence that they contain proteolytic enzymes and are, therefore, attracted to sites of protein invasion as a protective mechanism. The increased numbers in the blood stream are suggestive of allergy, and their

*Table 40*  
DIFFERENCES BETWEEN ATOPIC AND NONATOPIC ASTHMA

	<i>Atopic Bronchial Asthma</i>	<i>Nonatopic Bronchial Asthma</i>
Family history of atopy.....	Usually positive	Usually negative
Past history of atopy.....	Usually positive	Usually negative
Skin reactions.....	Usually positive	Usually negative
Antiatopic therapy.....	Usually successful	Unsuccessful
Age of onset.....	Early decades (1st to 3rd)	Later decades (3rd to 9th)
Intractability of symptoms (status asthmaticus).....	Unusual	Frequent
Blood eosinophilia.....	Moderate	Moderate to intense
Complications.....	Bronchitis Emphysema	Emphysema Bronchitis Myocardial changes Pleurisy with effusion Periarteritis nodosa
Prognosis (relief of symptoms).....	Good	Uncertain
Mortality.....	0-1 %	5-10 %

appearance in uninfected nasal and bronchial mucus is diagnostic.

The skin test, ever since the introduction of clinical allergy, has been the keystone on which its practice has depended. In the earlier years, a negative reaction implied that the allergen at fault had not been used, and it became conventional practice to do many hundreds of tests on each patient. When this method failed to give a reaction in a substantial percentage of cases, or gave positive tests which had no relevance, the fallibilities of the skin test became apparent, and they are several. In the first place, antibodies are not evenly distributed throughout all cells, and can be demonstrated in but few tissues, particularly those of the upper and lower respiratory tracts, the skin, and some of the gastrointestinal organs. Moreover, it is unusual for antibodies to be present to the same degree in a given case, even in these tissues. Thus, a child who has urticaria from eating strawberries usually does not have asthma, or vasomotor rhinitis, or abdominal cramps, although all organs are exposed to the circulating allergen; and antibodies may be confined to the skin. Likewise, antibodies may reside in the bronchial mucosa, but not in the skin. In that case, contact with a specific allergen will induce bronchial lesions, but no skin reaction is possible. This explains why only some 60 per cent of patients with asthma give positive skin tests; the remainder either are atopic without antibodies in cutaneous cells, or belong to the nonatopic group. Likewise, in vasomotor rhinitis,

allergic headache, and gastrointestinal allergy, positive skin reactions are frequently absent. In hay fever, there is usually a closer correlation.

Frequently, positive reactions appear which have no relevance. As a matter of fact, it has been shown that some 25 to 30 per cent of nonatopic individuals give positive tests to standard lists of common allergens. To put it differently, their cutaneous cells contain antibodies. Presumably, these are deposited there after contact with circulating allergens, but in no other tissues have such antibodies to atopsins been demonstrated in normal subjects. These antibodies remain unrevealed unless they are exposed directly to concentrated antigens as used in skin testing.

Positive reactions frequently vary in size when tests are done at intervals, and on different parts of the skin, so that a 4+ reaction on the back may be a 2+ on the arm, or a 2+ response on the back may be negative elsewhere.

With these conditions, the skin test is a valuable asset. A positive reaction indicates the presence of an antibody which may accidentally be revealed but has no relevance, or such an antibody may be the one responsible for symptoms. All reactions, therefore, should be confirmed either by excluding the suspected allergen from contact with the patient and noting subsequent improvement, or by exposing the patient and observing resultant symptoms. The skin test is very valuable, also, in the determination of the dilution of extract to be used in treatment, as will be pointed out.

One fact which has greatly simplified skin testing has been the revelation that, in the great majority of patients with atopy severe enough to require medical attention, comparatively few allergens are responsible for symptoms. These are the ones encountered continually, as house dust or milk. Some appear under particular circumstances, as dander from household pets, cosmetics, exposure to insecticides, and seasonal pollens. Since the number of allergens usually at fault is comparatively small, standard lists of testing materials have been reduced from many hundred to two or three score or less. Such lists may be found in standard texts, as will the technics of testing (see References).

Since symptoms occur only on contact between an allergen and its specific antibody, and only comparatively few allergens are usually involved, the elicitation of a careful history is coming to supersede the skin test as the most important diagnostic procedure. From the standpoint of differential diagnosis, a family history of atopy would tend to distinguish the wheezing in bronchial asthma from that of chronic bronchitis or cardiac asthma, and vasomotor rhinitis from the common cold. A carefully secured history is particularly useful in locating the offending allergen. For instance, sneezing that appears only at night and early morning hours is usually due to feather pillows, or asthma that occurs indoors suggests house dust. The cause of urticaria that appears periodically may often be identified by a history of food or drug ingestion just previous to each attack, and in hay fever the date of onset of symptoms and their duration will usually identify the pollen at fault. If symptoms are continuous, a common food or pollen or several allergens may be involved, or there may be complicating infection. A dietary history likewise complements skin testing, for a positive reaction to a food rarely eaten usually has no bearing, whereas one to milk in substantial quantity would be highly suggestive.

Treatment by exclusion of the offending allergen, where possible, is the most constructive and satisfactory. Here again, the older conception that avoidance must be absolute to be successful, is yielding to the realization that hypersensitivity is quantitative. A child may be so exquisitely sensitive to egg that a crumb of cake containing it will cause pronounced symptoms, whereas another child will have asthma if he drinks a quart

of milk a day but will be unaffected by cream, or ice cream or butter. In the great majority of instances, hypersensitiveness is not extreme except, perhaps, in hay fever. Although the principle of complete exclusion is still practiced extensively, a more liberal attitude, together with less emphasis on the skin test and more on history taking, is simplifying the practice of allergy.

The determination of which allergens to exclude, and how rigidly, is a matter of trial. In an adult patient with asthma, inhalants rather than foods are usually at fault. Under proper circumstances the problem can usually be worked out satisfactorily. The best method is brief hospitalization in a room devoid of rugs, heavy drapes, and upholstered furniture, with pillows encased in impervious material and the mattress similarly covered. Cosmetics are excluded and a regular diet allowed. If asthma is uncomplicated and due to inhalants, it will clear entirely in two or three days. It then becomes a matter of duplicating such a bedroom at home. If asthma does not reappear, nothing further need be done; if it does, dust elsewhere in the house is suspected. Here again, in many patients not exposed to dust in the bedroom during sleeping hours, unless confined to the house, the intermittent exposure during the day may not be sufficient to cause symptoms.

If symptoms persist in a dust-free room, a diet is given which is restricted to some 12 or 15 foods not commonly eaten. Relief would then point to incrimination of one or more excluded foodstuffs, and by gradual addition until symptoms reappear the problem can usually be worked out. Should symptoms persist, the elimination diet is readjusted, and if that fails the asthma is either complicated by bronchitis or is the intrinsic or nonatopic type.

When symptoms are periodic with substantial intervals of freedom, again a dietary and environmental history of exposure during the previous 12 to 24 hours is usually much more revealing of suggestive allergens than skin testing alone.

These methods of selective elimination may be applied to all atopic disorders. When allergens cannot be avoided, some may be extracted in simple solvents and injected. This is the standard method of the treatment of hay fever. With house dust and occupational inhalants, as animal danders (farmers), etc., inoculations are likewise

often effective. Foods are avoided, and their extracts no longer injected.

The beneficial results in hay fever when pre-seasonal injection treatment was used, were believed to be due to the process of desensitization, wherein each injection given in increasing amounts presumably neutralized more and more antibody until little was left to react with pollen when it appeared in the air. Then it was found that, when symptoms were reduced, positive skin reactions were usually just as large after such treatment as before. Dilute pollen extracts applied to the nasal mucosa likewise caused a marked reaction. Although improved, the patient was apparently as sensitive as before specific therapy was applied.

This problem seemed solved by the discovery of another antibody, the so-called "blocking" or "thermostable" antibody, since it is heat-resistant in contrast to reagin. Blocking antibody is not present in untreated patients but is induced in both normal individuals and those with hay fever as a result of injections of pollen extract. A theory was advanced that both this antibody and reagin compete for atmospheric pollen, but blocking antibody has a stronger avidity for it, and by combining with it prevents its contact with reagin. Lack of contact with reagin prevents liberation of histamine, and the patient, although protected, remains hypersensitive. To prove this theory, an attempted correlation between improvement in symptoms and titer of blocking antibody was made recently. There was no relationship whatever, and the reason for improvement following specific therapy remains unknown, and probably will continue so until the many complicated factors that enter this immunologic problem become simplified.

With this background, the disorders of atopy will be considered.

### BRONCHIAL ASTHMA

This is the most important of the atopic group because it is frequent and the most severe in its complications, with a substantial death rate.

The bronchial lesions embrace all those of atopy: edema, smooth-muscle spasm, and increased secretion from mucous glands. Each of these contribute to narrowing of the airways, particularly at the level of bronchioles with diameters of 2 to 8 mm. These smaller structures have no cartilage which might limit constriction. As

air is forced past this obstruction, wheezing appears and, on auscultation, musical rales from sticky mucus are heard.

The force of inspiration—namely, the contraction of the diaphragm and the levators of the ribs—greatly exceeds the weaker one of expiration: lung elasticity, contraction of costal depressor muscles, accessory squeeze of abdominal muscles, and peristaltic movement of the bronchi. Consequently, air is more easily inspired than expelled, and during an asthmatic paroxysm it becomes partially trapped in the alveoli which distend to produce acute emphysema. This situation produces the picture of an acute asthmatic attack: dyspnea, particularly expiratory, with wheezing and rhonchi, and the thorax in the position of extreme inspiration. Cyanosis is present, for the lungs are so distended with residual air that the midpoint of breathing is raised substantially. Moreover, the distended lungs crowd the diaphragm downward toward its position of contraction, and, with the chest in the inspiratory position, the vital capacity is markedly reduced. Unless chronic emphysema is present with destruction of alveolar walls, there is probably little interference with diffusion into the blood of oxygen that reaches the alveoli. When advanced emphysema exists, a superimposed asthmatic attack may cause a marked reduction in oxygen saturation of the blood.

The distended lungs cause the hyperresonance elicited on percussion, and this, together with wheezing and rhonchi, makes determination of cardiac outline and audibility of heart sounds difficult. The arterial pressure is usually normal or somewhat depressed during an asthmatic paroxysm. However, the venous pressure may be elevated because blood flows less freely from the venae cavae into the atria as the intrathoracic pressure becomes less negative when acute emphysema is fully developed.

From the foregoing, typical features of a case of uncomplicated bronchial asthma are as follows:

Since in most instances asthma is atopic, the history will frequently reveal a positive family history of atopic disturbances. Moreover, such disorders in the patient's past or concomitant history often are to be found, for it is common for an asthmatic to have eczema in infancy or associated hay fever. To state it otherwise, antibodies may appear in sufficient quantity in more than one tissue in such an individual, to cause symp-

toms on contact with the specific allergens involved. So frequently are both the upper and lower respiratory tracts affected that the patient will often state that nasal stuffiness with watery discharge is associated with his asthmatic paroxysm. A history of the present illness will probably reveal the onset of asthma to have occurred before the age of 20 years. The attack usually appears in the night. There have been several explanations for this: frequent hypersensitivity to some allergen in the bedroom; enhancement of vagal influence during sleep, and the accumulation of bronchial secretion. The last seems the most probable. As the paroxysm develops, the patient assumes a characteristic attitude by sitting upright and bending a little forward, with his elbows resting on a table or window-sill. This position tends to elevate the ribs to assist inspiration, and, by bending forward the abdominal contents crowd the diaphragm from its low position (that of contraction) upward so that it has more opportunity for excursion. Typical physical signs appear, as noted above, and at the height of an attack air hunger may be great.

The attack may last for hours or, with status asthmaticus, for days. If terminated abruptly by epinephrine, the patient who has coughed up but a little clear, thin, mucoid secretion will then produce thick, clear, gelatinous, and, at times, nummular mucus, which is the most important element in the bronchial obstruction. This mucus comes from glands in the bronchial wall, although a little is contributed by goblet cells in the mucosa. If one shakes this mucus vigorously in a Petri dish containing physiological saline solution, it will fragment, and, as the plate is held against a black background, small gray masses and tiny spirals will appear. The former are the so-called pearls of Laennec and the latter, Curschmann's spirals, which are unraveled pearls. They are casts of small bronchioles molded by bronchial constriction. If placed under a cover glass unstained on a microscopic slide and observed under low power, the strands of the spiral may sometimes be seen. Enmeshed in them are leukocytes, almost all of which are eosinophils. Such a demonstration is diagnostic of uninfected bronchial asthma.

The blood eosinophilia is of but moderate degree, as a rule. Between paroxysms in a patient with uncomplicated asthma, there are no signs

or symptoms, since the lesions are completely reversible. A positive skin reaction may appear and a slight blood eosinophilia persist.

The characteristics of nonatopic or "intrinsic" asthma that remains uncomplicated are indicated in table 40. Clinically, three types may be identified. The first is the most benign. It consists largely of persistent cough with the production of clear mucoid sputum containing eosinophils with but few pus cells and few bacteria in washed specimens. There are few if any true asthmatic paroxysms, but distant wheezing and rhonchi usually can be heard on auscultation. On exertion the patient becomes aware of his wheezing. The term "asthmatic bronchitis" has been applied to this condition, which may persist for years. As in atopic asthma, there may be an associated vaso-motor rhinitis.

The second type is the most serious. A typical example would be as follows: A patient of forty with no allergic background begins to cough at night or in the early morning hours, and soon develops the characteristics of the first type. Some months after onset, a true asthmatic paroxysm occurs. These attacks grow in frequency and severity until status asthmaticus, intense intractable asthma, appears. Such paroxysms may continue for days, recur frequently, and become more and more resistant to treatment. The duration from the onset of cough to the development of status asthmaticus may be no longer than one year. Such asthma has marked effects on the patient. During prolonged attacks he eats and drinks but little, and loss of weight may be considerable. Despite heavy doses of sedatives, he cannot sleep. The extremely acute emphysema leads to an advanced chronic type in a surprisingly short time, particularly when the onset is later in life. When a severe paroxysm supervenes on such lungs already permanently distended and with markedly reduced vital capacity, cyanosis may be great and air hunger intense. General debility increases, dyspnea is constant, and the patient dies in a paroxysm or from superimposed acute pulmonary infection. It is of interest that no evidence of chronic bronchial infection is elicited in this type.

Another patient may have this type of asthma for years with periods of recurrence and recovery. At times recovery seems complete. The prognosis is entirely unpredictable.

The third type of nonatopic asthma is charac-

terized by the presence of bronchial infection. This is the most common form. Whether infection complicates existing asthma or actually induces it is a moot question. These cases are sometimes referred to as "bacterial asthma." However, the assertion that asthma is an expression of bacterial allergy is wholly unfounded. As will be seen, the lesions and immunologic mechanism of known bacterial allergy are totally different from those of atopy or disorders of the nonatopic group. It is far more probable that this type is essentially intrinsic, but complicated by bronchial infection which, by producing purulent secretion, adds insult to bronchi already damaged. Relief of symptoms may occur by treating the infection and by simultaneous antiasthmatic therapy.

Post-mortem examination of the severe type of nonatopic asthma reveals a remarkable picture. As the lungs are sectioned, many bronchi are seen to be completely occluded by plugs of tough, inspissated mucus. On longitudinal section in some cases, bronchial casts are seen. Microscopic examination reveals the same situation in the smaller bronchioles, which may be completely plugged with mucus in which eosinophils are enmeshed: or, when a lumen does appear, it is markedly reduced. Little is known about the production of this material. It seems to differ in its consistency from the more fluid or softer mucus produced in typical early atopic asthma. Examination of the mucous glands reveals abnormal structures in that not only are they enlarged, but cellular degeneration may be seen at times. Although hypertrophy of bronchial muscle appears which probably increases bronchospasm, there is little doubt that suffocation occurs principally from the barrier of mucus between inspired air and the alveolar capillaries.

Atopic asthma may be complicated by bronchitis, and the picture then simulates that of the bacterial type of nonatopic asthma. The distinction can only be made by applying the criteria listed in table 40.

In both atopic and intrinsic asthma, paroxysms may be induced temporarily from nonspecific causes such as inhalation of dust, cold air, or irritating fumes, or by exertion. This is explained by hyperirritability of the sensory fibers in the bronchial mucosa, which sets in motion a reflex arc involving the hypertrophied bronchial musculature with its increased tonus.

Routine laboratory procedures in all cases should include the following: The most common form of skin test is the cutaneous method, wherein powdered prepared allergens are placed on a series of cuts made through the superficial skin layer and dissolved in a drop of 0.1 N NaOH. Reactions are read in 15 minutes. This method is the safest and simplest, but less sensitive than the intracutaneous, in which dilutions of extract are deposited in the superficial skin. Sterile technic is required. Also required are a tuberculin-type syringe and needle for each test, properly standardized extracts with replacement of deteriorated ones, and, above all, training in performing the test and knowledge of dealing with untoward reactions which may cause violent symptoms and death. The details of testing and cautions involved may be found in standard texts (see References). The passive transfer test (see p. 444) is useful in dermatologic conditions where no suitable areas for direct skin testing are available, and particularly in young children who will not submit to testing or where exquisite hypersensitivity is suspected. A positive reaction by this method indicates the presence of reagins in the blood of the patient, and these occur only when he has corresponding positive skin reactions.

A most significant test is examination of the sputum. This requires isolation of a small bronchial plug of mucus which can be secured only when it is separated from the sputum mass by vigorous shaking in saline solution. Once on a platinum loop, its surface is washed in fresh saline and it is then smeared on a glass slide and stained with Wright's blood stain, or preferably by eosin followed by methylene blue. In noninfected asthma, myriads of eosinophils and a few epithelial and pus cells on a blue background appear. With superimposed infection, in addition to eosinophils, many pus cells and bacteria occur.

Fluoroscopic observation of the chest between paroxysms is important in determining the position and excursion of the diaphragm. In the presence of early emphysema, even before the vital capacity is reduced, the diaphragm will be somewhat lowered by the distended lungs and its excursion that much restricted. In advanced emphysema, it is flattened and motionless or may exhibit paradoxical movement as costal breathing alone remains and draws it upward on inspiration. The lung fields then show increased trans-

illumination with bronchial markings obscured. The cardiac outline is spindle-shaped as it is elongated by its attachment to the lowered diaphragm. If enlarged, cor pulmonale or a coincident cardiac lesion is present.

Determination of vital capacity in the absence of cardiac compensation, fortunately a rare complication, is a rough measurement of pulmonary function. It is made between paroxysms. It may be reduced temporarily by intercurrent bronchial infection and lowered permanently by emphysema. In following a patient over a period of time, serial readings are helpful.

An electrocardiogram, sputum culture, and other laboratory proceedings are carried out when relevant.

**Differential Diagnosis.** Asthma or wheezing occurs with bronchial obstruction from any cause. The one that simulates true bronchial asthma most closely is bronchitis. The absence of paroxysms of wheezing (except, perhaps, mild ones after exertion), chronic cough with purulent sputum, absence of eosinophils and of excessive glairy mucus, and, therefore, but few musical rales, should give little difficulty in distinguishing the two conditions. However, it is surprising how many patients with bronchitis are sent to allergy clinics because of mild constant wheezing due to bronchial obstruction from increased secretion, and mild bronchospasm from hypertrophied bronchial musculature which occurs in chronic bronchitis as well as in asthma.

Cardiac asthma may closely simulate bronchial asthma in its paroxysmal nocturnal attacks of wheezing. The obvious underlying vascular or cardiovascular pathology gives the clue. When both types of asthma are associated—a rare occurrence—the eosinophils and mucoid sputum will be present in addition to the lesions in the heart. Cardiac asthma rarely occurs with cor pulmonale.

In emphysema there is some bronchospasm, and wheezing occurs on exertion, but since there is no moisture, no rhonchi are present.

Bronchial obstruction from carcinoma or other isolated lesions induces wheezing, but this is usually more in the nature of a stridor, as larger bronchi are often involved. On physical examination, signs are heard loudest during inspiration, and constantly over the site of the obstruction.

**Treatment.** In the treatment of bronchial asthma it is well to have the following general

facts in mind: In the atopic type symptoms usually begin in the earlier years of life, and the capacity to develop antibodies to allergens tends to diminish with succeeding decades. If one can tide the patient over this early period, the problem usually becomes simple as hypersensitivity diminishes. There are, of course, exceptions to the rule. Unfortunately, one cannot apply safely the principle that asthma is self-limited without treatment, since emphysema is one inevitable consequence. An analysis of a series of asthmatics who have had symptoms continually for more than 10 years revealed that essentially all had developed emphysema. It is this, rather than temporary paroxysms of wheezing, that causes permanent crippling. Two patients with bronchial asthma have been observed. The only therapy was epinephrine, self-administered at the onset of daily paroxysms. After 20 years, neither patient has emphysema, obviously because acute attacks were prevented at the time of onset. As in so many other diseases, it is therefore important to treat asthma early.

Treatment may be specific or nonspecific. The former is directed toward the immunologic process and the latter is applied to any case regardless of cause. It cannot be overemphasized that symptoms of atopy occur when an allergen comes in contact with its specific antibody, and, conversely, unless such contact occurs there can be no symptoms. This entails the detection of the allergen at fault by means already outlined, and its avoidance. When the allergen is known and cannot be excluded, as with pollen asthma, injections with allergenic extract are indicated. These are described under "Hay Fever." Protection secured thereby, unfortunately, is but temporary.

In atopic asthma in which the allergen cannot be found, or in occasional cases in which there are several and all cannot be excluded, or in the intrinsic type, treatment is directed to the paroxysm itself. As already stated, the essential bronchial lesions can be produced by acetylcholine which is released on stimulation of the vagus nerve, and prevented by sympathomimetic drugs as epinephrine and ephedrine. The former is dramatically effective in promptly relieving an attack. There are several facts to keep in mind regarding the administration of epinephrine. The first is that much more than is needed is usually given, and side effects such as tremor and palpi-

tation are produced. Usually 0.2 to 0.3 ml. is sufficient if given early. Although in status asthmaticus the dose must be increased, the drug is not habit-forming and small doses may remain effective indefinitely. Prolonged use has revealed no proved harmful effects. As a matter of principle, it is far better to employ epinephrine at the inception of a paroxysm when a few minims will suffice, than after the development of an attack when more is needed, for the emphysema that follows repeated stretching of the alveoli is far more harmful than the drug itself. The disadvantage of hypodermic injection may be met by an aerosol of 1:100 dilution administered by a nebulizer. This is a useful device. Ephedrine and its several compounds and related substances are less effective, except in children, unless wheezing is mild. Given at bedtime in doses of 75 mg. (for an adult, with a like amount of amytal), it may prevent an attack or abort one that has begun.

A very effective drug in relieving asthma is ethylenediamine or aminophylline. This acts directly on smooth muscle and releases contraction. As the bronchial lumen widens, the thick, tenacious mucus is more easily expelled on coughing. Aminophylline alone is not very effective orally, since it cannot be given in large amounts, and is best administered intravenously in doses of 0.25 to 0.5 Gm. This is given preferably in a few hundred milliliters of physiological saline or glucose solution. Vomiting and other side reactions are thus usually avoided. In severe cases the dose may be repeated every eight hours. A very useful form of administration is by suppository, of which there are several proprietary products. By inserting one rectally, the use of hypodermic epinephrine may be avoided.

Perhaps the most useful drug in bronchial asthma is potassium iodide, for it directly attacks the principal lesion—the plugs of mucus in the bronchial tubes. It is effective only if given in generous doses such as 0.5 Gm. every three hours for the first few days. The elixir of lactopepsin is a good vehicle.

Armed with epinephrine, ephedrine, aminophylline, and potassium iodide, one need consider only oxygen and sedatives as further therapeutic agents, and may eliminate the many other drugs recommended.

In inverse order of severity, one would use ephedrine and potassium iodide for mild wheezing, epinephrine and aminophylline for acute at-

tacks, and a combination of all for status asthmaticus, wherein symptoms are intractable to conventional treatment. The latter is the most difficult situation to treat, and vigorous measures are essential. It must be realized that patients with status asthmaticus are very ill. The continuous extreme dyspnea which may persist for days not only prevents sleep and adequate nourishment but causes extreme mental anxiety. The fear of impending death and the discouragement of failure of all treatment create an intense emotional situation. Usual sedatives, as barbiturates, even in generous doses, have but temporary effect, and even anesthetics such as avertin give relief of short duration. The recognition of this situation is the key to successful treatment, for once the patient's senses have been obtunded for 24 to 48 hours, the status is broken and thereafter conventional drugs are again effective.

Given, then, a patient in status asthmaticus, the first consideration is to get him to sleep. Morphine must never be used, for it causes bronchospasm and has been held responsible for many deaths. "Demerol Hydrochloride," however, may be used with safety in 100 mg. doses. Paraldehyde has proved by far the best drug. Rectal administration of 15 to 30 ml. in 50 to 100 ml. of olive oil will soon put the patient to sleep, but he usually awakens in a few hours and must have more. He is placed immediately in an oxygen tent, or the gas, preferably combined with helium, is given through a mask. Intravenous aminophylline in 500 ml. of 10 per cent glucose solution is administered, for dehydration is usually present; this is repeated twice during the first 24 hours. The patient is aroused every three hours to take liquid nourishment and 0.5 Gm. of potassium iodide in solution. Within a day or two, definite improvement occurs, and epinephrine, which had lost its effectiveness, may again be employed in conventional small doses. Aminophylline is injected only once a day, but iodides are given vigorously. As the patient gradually awakens, symptoms have been greatly reduced, to his enormous relief, and he is left only with fear of another such attack. At this stage phenobarbital is useful. The demonstration of the influence of the emotional element on paroxysms has given validity to psychotherapeutic treatment, which, when properly applied to severe asthmatics between attacks, may be very helpful.

Moreover, psychotherapy in the treatment of

various atopic diseases is receiving increasing attention, but as yet there has been no clear indication whether atopic individuals are, in the main, psychoneurotics. If this be true, psychotherapy may have an important place. Most allergists believe that psychoneurosis is an incidental rather than a primary factor in atopy.

Bronchial asthma complicated by infection presents a special problem, for pus in the bronchi is an added irritation and is responsible for the intractability of many cases. The treatment is that of bronchitis. Chemotherapeutic agents such as penicillin may be very useful, but should be given in large amounts. The drug to use may be determined by culture of the sputum. At the end of a course, asthma is frequently much improved and will respond promptly to iodides and ephedrine, which should be continued well beyond cessation of symptoms and then withdrawn slowly. Aerosol penicillin has proved disappointing. It is these cases with chronic bronchial infection that do well in perpetual warm weather. Otherwise, the only advantage of climate to asthmatics is that the nonspecific irritation of cold air, fog, smoke, etc., is avoided, as is an occasional specific allergen that had not been detected.

The occasional benefit of a large variety of physical and chemical measures advocated for the relief of asthma is recognized, but all are too inconsistent in their effect to be recommended.

**Complications.** The inevitable complication of prolonged bronchial asthma is pulmonary emphysema. It is this, rather than asthmatic paroxysms which in the earlier stages are reversible, that permanently cripples. Bronchial infection is also very common, as has been mentioned. One circumstance where this is noteworthy is in asthmatic children with pollinosis. The frequent episodes of winter colds with coughing begin soon after the ragweed hay fever season and recur in the spring. Apparently, the boggy nasal and bronchial mucosa is good soil for bacteria, for with adequate treatment of the hay fever, winter infection may appear far less frequently.

Cardiac complications of asthma are present only after emphysema has become advanced when cor pulmonale may occur, although the signs of emphysema and cardiac failure may be identical. Dependent edema, due probably to increased capillary pressure and anoxemia, is seen occasionally in advanced emphysema in which the heart at autopsy shows no demonstrable

lesion. Dyspnea on exertion, reduced vital capacity, cyanosis, increased venous pressure, a liver displaced downward by the low diaphragm, basal rales from bronchitis, and distant heart sounds occurring in emphysema may well simulate signs of cardiac insufficiency.

Periarteritis nodosa is a rare complication, but it should be noted that when it does occur it is associated with prolonged or severe attacks. It is almost always identified with the intrinsic type, but exceptions have occurred. This remarkable condition was first found to be associated with bronchial asthma in 1914. The case described also presented a blood hypereosinophilia. A collection of similar cases reveals that this triad of bronchial asthma, periarteritis nodosa, and hypereosinophilia occurred in something less than 20 per cent of all reported cases of periarteritis with post-mortem examinations. Moreover, with few exceptions, the increased eosinophilia appeared only in the presence of bronchial asthma. The differential counts in the reported series gave values ranging between 11 and 82 per cent, with an average of over 50 per cent, in contrast to less than 3 per cent of eosinophils in the blood of patients with periarteritis nodosa without asthma. It is of interest that the arteries involved are by no means confined to the lungs. In these cases an occasional pleurisy with effusion is encountered in which the cellular elements are almost all eosinophils.

#### HAY FEVER

It is estimated that over 2 per cent of the population of the United States, or some 3,000,000 people, suffer from hay fever. Only a small fraction is adequately treated and, although many cases are mild, the degree of disability is considerable. Unfortunately, good treatment is time-consuming, only partially effective in most cases, and is temporary.

The reason for the large incidence of pollinosis is the high degree of antigenicity and enormous prevalence of ragweed pollen. Although these pollen granules are so volatile that they may be blown some 50 miles from their source and thus nullify local control, it is estimated that about 250 tons fall to earth during a single season. The antigenic fraction of pollen has never been isolated, and, although it contains some protein, the amount is not comparable to such strong antigens as egg albumin or the serum proteins

with their great molecular masses. However, pollen extracts produce antibodies to a high degree. Each locality has its pollen seasons and indigenous plants responsible for them. On the northeastern seaboard, trees pollinate in the early spring, then a few grasses such as timothy, red top, and sweet vernal, then plantain and ragweed and a few other weeds. There is little or no ragweed in Florida or the West Coast, but hay fever is prevalent at seasons corresponding with local pollinations. The country has been adequately surveyed in this regard and data are available in the literature. Although many such reports record a large number of pollinating plants, other than a comparatively few trees, weeds, and grasses, most are unimportant in the etiology of hay fever.

A patient with hay fever is one who has the capacity to deposit antibodies in his nasal mucous membranes after repeated exposure to pollen antigen. It usually takes several pollen seasons to effect this. If his allergic heredity is strong, and exposure is adequate, symptoms may appear in early childhood. In some it may take twenty seasons or more before antibodies appear. When they do, then further contact with antigen presumably causes release of H-substance, leading to local edema. In the great majority of patients antibodies are deposited in the skin, and reach the blood stream, so that direct skin tests and those for circulating antibodies (passive transfer) are usually positive. At times, especially in children, antibodies appear likewise in the bronchial mucosa, so that asthma is not an infrequent complication at the height of the season. When pollens leave the air, the lesion disappears and a reversion to normal-appearing structure occurs, but the antibodies are still there and disappear only as the patient gets older, although active symptoms in the fifth and sixth decades are not uncommon. Confronted with such a situation, treatment becomes difficult. In severe cases no drug is adequate, and one of two choices is offered; namely, to move out of the pollen area, or to take injections with pollen extracts. The first measure is preferable but usually not possible, for it entails a yearly sojourn of weeks or months far from home; and then there are such pollens as timothy from which one can escape only by going to remote areas. Injections with pollen extracts remain the most successful therapeutic measure, provided they are properly adminis-

tered. To purchase commercial products of a given strength and schedule of injections may be adequate for some patients, but the degree of hypersensitivity varies so much that standard treatment sets may be too dilute or too concentrated for effective results.

Given a patient with hay fever who is to receive such treatment, it is first necessary to correlate the pollen which gives his positive skin reaction with the date of onset of symptoms. Then the proper plan is first to estimate the degree of hypersensitivity of the patient. This may be done by the skin test as a working basis. As stated previously, the incidence of relevant skin reactions in hay fever is high. An intradermal injection of 10 protein nitrogen units<sup>1</sup> (which gives no reaction, whereas 100 units gives mild response) identifies the degree of hypersensitivity, and treatment may be begun with an extract of 100-unit strength. If 10 units gives a pronounced reaction, it is too strong a dilution for initial injection.

For years it has been conventional to begin treatment a few months before the pollen season and, by increasing the strength and amount of extract, attain a high dose by the time pollen appears. Injections may be discontinued then or the dose reduced and continued throughout the season. Unfortunately, antibodies so induced fall off so that the following year the same process is repeated. A more satisfactory arrangement is perennial treatment wherein, once high levels are attained, they are kept there by injections given every two or three weeks throughout the year. Coseasonal treatment begun at the onset of the season, wherein small amounts are given at frequent intervals, has little to recommend it.

Treatment with pollen extract is surrounded with difficulties. To begin with, it is dangerous in unskilled hands. The principle of treatment is to begin with a safe initial dose and attain a high final dose, but if an increment is too large, the patient may react violently with suffusion of the face, generalized urticaria, asthma, and peripheral vascular collapse. Death has occurred from skin testing wherein highly sensitized individuals were injected with small amounts of the allergen at fault, as well as from too large a prophylactic dose. Emergency treatment consists of placing a

<sup>1</sup> Other standardizations are "nonprotein nitrogen units" and "pollen units," which represent weight-volume ratios.

tourniquet proximal to the injection, inserting epinephrine into the wheal and just above it to delay absorption of the allergen via the lymphatics, and administering more epinephrine subcutaneously; oxygen is needed occasionally.

Unfortunately, treatment with pollen extract remains empiric. Presumably it fails to desensitize the tissues which still contain reagins, nor has there been any correlation of symptoms with the blocking antibody which appears as the result of treatment. To indicate the complexity of the problem, it has been found that in a treated patient during the pollen season, ragweed antigen, blocking antibody, and reagins are all present at the same time in the circulating blood. Consequently, schedules of treatment are arbitrary; some allergists give a few injections, others a great many; some attain very high final doses, others moderate ones; and the same discrepancies occur with intervals between injections, the use of single or mixed antigens, and preseasonal and perennial treatment; and yet the reported results are about the same. About 20 per cent are completely relieved, another 60 to 70 per cent have satisfactory relief, and in 10 to 15 per cent the treatment is a failure. Conventional texts contain the details of testing and treatment.

Supplementary therapy consists of pollen exclusion and drugs. Windows are closed or screened with layers of moist cheese cloth to catch pollen; air filters, air conditioning, masks, and nasal filters are used extensively.

Although ephedrine or one of its isomers, by mouth or as nose drops, was the drug of choice for years, the introduction of antihistamine drugs marketed as "Benadryl," "Pyribenzamine," "Neohetramine," and many others has been a decided advance. The standard dose is 50 mg. three or four times a day. Employment of these drugs in supplementing treatment with pollen extracts has made such therapy much more effective, and their use alone frequently alleviates symptoms in milder cases. The toxic effects of some of these substances limit their usefulness. "Neohetramine" seems to have less side action than others now available and may be taken in larger doses of 100 mg., five or six times a day.

It would appear that once a patient has attained a top dose which protects him satisfactorily by parenteral injections with pollen extract, perennial treatment supplemented with

antihistaminic agents when needed is the most satisfactory treatment at the present time.

### VASOMOTOR RHINITIS

Vasomotor rhinitis has the same symptoms and lesion as hay fever, but occurs on exposure to dusts or foods which also induce antibodies in the nasal mucosa. In adults, inhalants are far more frequent, particularly house dust. This allergen is a deterioration product of various fabrics, as mattresses, rugs, ozite pads, and similar household materials. Removal of these from the bedroom usually improves symptoms at night, but when this simple measure does not suffice, injections with stock dust extracts are at times effective. They are given under the same principles that govern treatment of hay fever excepting that treatment is prophylactic while symptoms are present. Other precautions are encasement of pillows and mattresses in nonpermeable covers, and removal of overstuffed furniture and cosmetics from the bedroom. If foods are suspected, methods of exclusion of those taken daily, or other conventional dietary manipulation to be found in standard texts, are employed.

At times the most rigid exclusion has no effect on symptoms. Under those circumstances infection may be present. This may be determined by staining smears of nasal secretion which in the presence of bacteria will show many eosinophils and myriads of pus cells. In such cases allergic symptoms will persist until infection is reduced.

There is a group of cases in which there is no infection and in which strict environmental control does not diminish symptoms, often severe. These patients are usually in the older age groups and conform to the pattern seen in intrinsic asthma. They are often intractable to all treatment.

Atopic vasomotor rhinitis is associated frequently with edema of the mucous membranes of the accessory sinuses which are cloudy on transillumination and simulate the picture of infectious sinusitis. This disappears as the nasal edema becomes less.

### GASTROINTESTINAL ATOPY

Of all the expressions of atopy, that of the gastrointestinal tract has been most abused. The contention that more than 50 different disorders affecting it are amenable to antiallergic treatment is entirely without foundation. There is no

question that edema of the gastrointestinal mucosa, spasm of the bowel, and excessive mucus may occur when antibodies to food allergens are present. A child highly sensitive to egg may vomit on ingestion of a small amount, and at times abdominal pain and diarrhea are definitely allergic in origin, but their proved occurrence in comparison to similar symptoms from other causes is not great. The concomitant presence of other allergies, as acute urticaria, at the time of attacks is highly suggestive. Skin tests are rarely helpful and treatment consists of elimination diets.

### HEADACHES

Here again, statements that a substantial percentage of migraine is due to allergy is far from true. As a matter of fact, true migraine with its aura is rarely proved to be due to allergy. There is no question, however, that allergic headaches occur not infrequently. These are of two types. The first is secondary to allergic vasomotor rhinitis, wherein the nose is blocked and the sinus mucous membranes swollen. The second, more usual type occurs from the ingestion of foods. Unlike asthma and other atopic disorders wherein those foods eaten frequently are at fault, atopic headaches are often due to such ingestants as chocolate, nuts, onion, and spices. Moreover, sometimes a mere trace of these, as rubbing the salad bowl with garlic, is sufficient to cause headache. This makes exclusion diets difficult, as they must be absolute. Skin tests are usually unrevealing.

### DERMATOSES

Acute urticaria with angioneurotic edema may be intense after the ingestion of foods to which one is sensitive. Lesions may also occur occasionally from contact with silk and other fabrics. Drugs may likewise cause urticaria, but here the mechanism is different, as will be described. Attacks are self-limited, but starch baths and antihistamine drugs are good treatment.

Chronic urticaria that does not respond to usual exclusion regimens is usually not due to atopy and may occur from a variety of causes. Chronic infection is one, and tooth-root abscesses should be suspected first. The lesion occurring in women at the menopause may disappear under treatment with estrogenic substances. Some cases are definitely due to hypersensitivity to heat or to cold. These are successfully

treated by daily thermal baths with corresponding increase or decrease of temperatures which will diminish such sensitivity. Some cases are due to dermatographia. Here, too, gradually increasing friction to the skin will often improve the lesion by reducing it and making it less pruritic.

Other cases remain intractable, and these too correspond to intrinsic asthma and vasomotor rhinitis. Antihistamine drugs are helpful, but only temporarily. Injections of histamine given on the principle that antihistaminic substances are thereby induced are of questionable value. They are given subcutaneously with an initial dose of 0.01 mg. of the base, and small increments are made daily for two weeks, then every other day, then twice a week. The top dose is 0.5 mg. Intravenous injections should be abandoned.

Eczema is one of the most troublesome of atopic disorders. It is important to distinguish the type to begin with. Neurodermatitis with lesions in the flexural folds occurring in infants and young children is usually atopic. That with more localized symmetric distribution, as over both eyes, confined to both hands, or the neck alone, occurs mostly in adults in contact dermatitis, to be described. Local and disseminated lesions may be caused by hypersensitivity to fungi, as seen in trichophytosis. A clearer distinction between these and detailed directions concerning treatment may be found in texts on dermatologic allergy (see References).

### OTHER ATOPIC DISORDERS

There are several manifestations of atopy such as conjunctivitis, labyrinthitis, purpura, and neuropathies, in addition to a large list of alleged atopic manifestations for which space is too limited for discussion in this chapter.

### SERUM SICKNESS

In about 80 per cent of patients receiving large doses of foreign serum, fever, urticaria (occasionally purpura), arthralgia, lymphadenopathy, and edema with retention of chlorides are common. These occur from about the fifth to the ninth day after the first dose, depending on the amount and frequency of administration. Occasionally, more severe manifestations, as peripheral neuritis, endocarditis, and sterile meningitis, are encountered. All these lesions appear to be reversible, although the degree of suffering and disability is considerable. The mechanism that

produces these changes has been stated in Chapter 36.

There is another way in which foreign serum affects man, and this is related to hypersensitivity from previous injection. With antibodies already present, injection of antigen may give an immediate reaction, as urticaria, asthma, and even collapse. This is particularly true in atopic individuals who may have a high degree of hypersensitivity to horse serum with circulating reagins to it. Such eases account for most of the reported sudden deaths from serum administration, and are responsible for the practice of inquiring whether the patient has asthma or hay fever, and of doing a preliminary skin test with 1:10 dilution of normal horse serum before larger doses are given. When a positive reaction is obtained, it has been demonstrated that with the utmost caution large amounts can be administered, provided the initial dose is extremely small (0.05 ml.) and gradual increments are given at frequent intervals.

Treatment is symptomatic, but dramatic results have been reported recently from the intravenous administration of proeaine in doses of 1 Gm., intravenously.

### BACTERIAL ALLERGY

Bacterial hypersensitivity is discussed in Chapter 36. It has distinct points of difference from those of atopy not only in the absence of circulating antibody, so that it, therefore, cannot be transferred, but also in the lesion which, instead of an immediate edema, is an inflammatory response characterized by cellular infiltration which takes 24 hours or more to develop fully. By that same process, contact with excessive amounts of antigen on the one hand causes immediate symptoms, but in bacterial allergy, as with tuberculin, the height of reaction is reached in two or three days. Conventionally, these two types of sensitiveness are referred to as the "immediate" and the "delayed," the "whealing" and the "tuberculin" types, and other designations to indicate their distinction. Both are examples of hypersensitivity, but expressed in different ways.

The important clinical consideration of bacterial hypersensitivity, be it with tuberculosis, or other infectious diseases wherein allergy plays a role, is that the symptoms of the disease are usually in direct ratio to the degree of allergy

present. A young patient with a small apical tuberculous infection may be quite ill with the classic signs of the disease because his tissues are highly allergic to tuberculin and only a little of this antigen is required to evoke an antigen-antibody response. Another patient with extensive lesions of the fibroid type may be anergic and unaware of his infection. Likewise, in brucellosis, when hypersensitivity is marked, a very small amount of injected vaccine will reproduce pronounced symptoms of the disease.

A decade or two ago it was a prevalent opinion that allergy was a function of immunity and served as a defense mechanism. Space will not permit elaboration of the many arguments to support that thesis, which is still adhered to by some. A swing in the opposite direction is now occurring, wherein allergy is considered to play no role whatever in this regard.

It should be pointed out that the subject of bacterial allergy, especially in regard to the various infections to which a positive specific skin test is secured, is a most complex mechanism. The arrangement of molecules which form the sensitizing element within the bacterial cell, about which little is known; the antigenicity of bacterial carbohydrates; and the almost complete lack of knowledge about fixed antibodies, demand a critical attitude. There is little question of the existence of hypersensitivity to bacterial products, but to assume, as is done too often, that intrinsic asthma associated with bronchial infection is bacterial allergy carries no justification.

### ALLERGY TO DRUGS

Drug allergy has come to be far more inclusive than the term implies, since it embraces a large variety of chemical substances with no medicinal application. No conventional designation for this large group of allergens has been accepted. There are two types of drug allergy—namely, contact dermatitis, wherein the lesion is caused by direct contact of the allergen with the superficial skin; and symptoms that appear after ingestion or parenteral injection. Its mechanism is discussed in Chapter 36.

Contact dermatitis is by far the commonest form of eczema in man. Given a patient with an eczematous lesion localized to both eyebrows, or axillas, or breasts, the diagnosis of contact dermatitis is evident, and the contactants suspected would be mascara, the material in dress shields,

and that in brassières; the latter two may be the ingredients of latex or rayon. Fur dyes cause lesions around the neck, shoe dyes about the feet, and bilateral symmetric eczema of the hands alone is always due to exposure to contactants. This type of eczema has a substantial incidence in industry where exposure to chemicals is constant.

A common experience is the application of an antipruritic ointment containing benzocaine or a variety of other contactants to an already established eczematous lesion, as neurodermatitis, with prompt relief. As the ointment is reapplied, in time it must be used more often and the eczema gradually becomes more intense because of a contact dermatitis from the drug superimposed on the original lesion.

Until the contactant at fault is revealed, little can be accomplished in terms of relief. A careful history of exposure of the part involved will usually suggest several contactants. Each of these is then applied to the skin as near to the affected area as feasible, by the technic of the patch test (see standard references), and the reproduction of the lesion by any of the material applied strongly suggests the discovery of the contactant at fault. Unlike routine skin tests with atopens where a few to which man is exposed most are used routinely, each case of contact dermatitis requires separate investigation.

Other than local treatment, little is available except in poison ivy and perhaps dermatitis to other plants, wherein parenteral injections of extracts, if carefully given, may be of considerable value (see References for technic of injections).

Of greater significance is allergy to drugs taken

internally. There is a similarity of symptoms of drug allergy to those of serum sickness. This is reflected in untoward reactions to sulfonamides, penicillin, and other drugs. Fever, urticaria, and arthralgia occurring after an interval of several days following first administration of the drug are manifestations identical to those of serum disease. Nirvanol, formerly used for chorea, gave similar manifestations; and as new drugs have appeared, so the incidence of allergy to them has become more apparent. In table 41 we begin to see that the symptoms and underlying lesions of hypersensitivity are a reaction pattern induced by totally unrelated antigens.

Perhaps the most important fact that recent knowledge of drug allergy has revealed is the danger of indiscriminate use of drugs, especially those known to induce hypersensitivity. Some 25 per cent of individuals to whom certain sulfonamide compounds were given, even after small initial amounts, became allergic to them.

This type of allergy is in the earlier stages of its development, and its mechanism is becoming apparent (Chapter 36). To be sure, drug reactions are much more manifest than recorded in table 41. Various skin eruptions, agranulocytosis, hepatitis, and other visceral lesions occur with various drugs and do not fit into this pattern. Whether these too represent hypersensitivity in terms of an antigen-antibody mechanism has not been established.

### VASCULAR ALLERGY

Necrotizing arteritis is a lesion common to all types of human hypersensitivity. It has been found with atopic manifestations as bronchial

Table 41  
SERUM SICKNESS "PATTERN" IN HYPERSENSITIVENESS TO VARIOUS DRUGS

	<i>Fever</i>	<i>Erythema</i>	<i>Urticaria</i>	<i>Arthralgia</i>	<i>Lymphadenopathy</i>	<i>Renal Disturbances</i>	<i>Arteritis</i>
Serum Sickness.....	+	+	+	+	+	+	+
Neoarsphenamine..... (Milian)	+	+	+	+	+	+	-
Nirvanol.....	+	+	+	+	+	+	+
Sulfonamides.....	+	+	+	-	-	+	+
Penicillin.....	+	+	+	-	-	-	-
Thiouracil.....	+	+	+	-	-	-	+

Table 42  
CLINICAL AND PATHOLOGIC MANIFESTATIONS COMMON TO SEVERAL TYPES OF HYPERSENSITIVENESS

	<i>Serum Sickness</i>	<i>Bacterial Allergy (Rheumatic Fever)</i>	<i>Allergy to Drugs</i>	<i>Vascular Allergy</i>
Fever.....	+	+	+	+
Urticaria	+	+	+	+
Purpura	+	+	+	+
Erythemas				
Arthralgia.....	+	+	+	+
Endocarditis.....	+	+	-	-
Myoendocarditis.....	+	+	+	+
Collagen Degeneration.....	+	+	+	+
Arteritis.....	+	+	+	+

asthma, in serum sickness, in bacterial allergy as rheumatic fever, and with sulfonamides and other drugs. In some instances it appears as fully developed periarteritis nodosa, in others, as in rheumatic fever, as arterial necrosis without the surrounding cellular inflammation of periarteritis, although this may occur.

The occurrence of periarteritis nodosa as a common factor of all types of allergy points to the participation of arteries and capillaries in the production of allergic lesions. This has been demonstrated in various ways both experimentally and clinically. In some instances antibodies evidently reside in the arterial walls, and lesions occur on contact with circulating antigens. In others, it is possible that capillary dilatation and permeability with the formation of edema, as seen in atopy, are produced through the release of H-substance from contact between antigen and antibody in contiguous tissue. These are problems of current investigation.

To sum up, it appears that although allergy may express itself in a variety of ways and thus be separated into types, there are certain newly developed facts which tend to tie them together into one process. First, the identity of symptoms of the serum sickness pattern appears in cases of bacterial allergy (rheumatic fever), and in hypersensitivity to drugs, although the antigens and antibodies involved may differ markedly from one another (table 42). Second, all allergic tissue reactions are reversible, as a rule. When exceptions occur, no matter what type is involved, collagenous degeneration of connective tissue and

arterial necrosis are common to all. Finally, it has been shown that a single injection of a large amount of horse serum into a rabbit has produced serum sickness, typical Aschoff bodies of rheumatic fever, and periarteritis in the same animal.

The development of clinical allergy during the past few years along the lines of broader concepts of human hypersensitivity is attracting increasing attention. It is doubtful whether the present practice of allergy will embrace these newer developments, but it will rather restrict itself to the specialized technics developed mostly for atopic disorders. Since allergy, however, is apparently applicable to such a wide field of medicine, it is probable that in the future it will become a closely integrated, rather than a specialized part of it.

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# 38

## Collagen Disorders

B. V. Jager

### Introduction

Polyarteritis Nodosa (Periarteritis Nodosa)  
Disseminated Lupus Erythematosus  
Scleroderma  
Dermatomyositis

### INTRODUCTION

The disorders polyarteritis nodosa, disseminated lupus erythematosus, scleroderma, and dermatomyositis, all of which will be considered here, are sometimes grouped together under the term *diffuse collagen diseases*. Discussed elsewhere are other diseases such as serum sickness (Chapters 36 and 37), rheumatic fever (Chapter 102), rheumatoid arthritis (Chapter 39), Loeffler's pneumonia (Chapter 36), and thromboangiitis obliterans (Chapter 242), as well as some of the so-called Erythema Group of Osler (erythema nodosum and multiforme [Chapters 221 and 222], anaphylactoid purpura [Chapter 226], etc.), all of which also may be included under this heading.

The expression *diffuse collagen diseases* is derived largely from the observation that an alteration in connective tissue is common to all of these conditions. Connective tissue includes the fibroblast with its delicate fibroglia fibrils and the intercellular substance consisting of collagen, as well as elastic fibers, reticulum, and an intercellular homogeneous ground substance which, in the normal state, is scarcely visualized with the usual histologic technics. Abnormalities of connective tissue may be proliferative, as evidenced by increases in the number of fibroblasts and by an increase in the amount of intercellular substance, especially collagen; or they may be degenerative, with changes in the fibroblast itself or in the intercellular substance. Thus the collagen may become granular or amorphous in appearance while the ground substance may become visible with the usual tissue stains. This combination may cause the collagen in stained tissue sections to resemble fibrin, the so-called fibrinoid degeneration. The altered connective tissue often is infiltrated with leukocytes so that inflammatory, proliferative, and degenerative changes may be present simultaneously. The location and

severity of the connective tissue changes vary considerably in the same disorder and, perhaps, vary somewhat more among the different disorders. Actually diffuse changes almost never occur. The walls of arteries contain much connective tissue, and alterations in such areas may lead to occlusion or, less commonly, to rupture of the vessel. The consequences of ischemia may contribute greatly to the production of the clinical manifestations. In scleroderma, the connective tissue changes are largely proliferative, while in polyarteritis nodosa and in disseminated lupus erythematosus, degenerative changes with variable inflammatory reactions are more evident. The inclusion of dermatomyositis in the group of collagen diseases is a moot point, since striated muscle fibers rather than connective tissue seem to be affected primarily in this disease.

The fact that alteration in connective tissue is a salient feature in these various disorders does not justify an assumption that there is a common etiologic factor. Additional evidence has been supplied, however, from studies of hypersensitivity reactions in man and in animals. Rabbits injected with certain types of foreign protein such as horse serum may develop histologic lesions similar to those encountered in patients with polyarteritis nodosa, rheumatic fever, or glomerulonephritis. Histologic lesions similar to those found in polyarteritis nodosa have been observed in man in association with hypersensitivity to horse serum and to certain simple chemicals. It must be borne in mind, however, that in experimental animals similar vascular lesions may be produced by administration of certain toxic chemicals, by experimental induction of hypertension, and by repeated administration of desoxycorticosterone acetate. Furthermore, in many individuals with polyarteritis nodosa, clinical evidence of hypersensitivity reactions has been lacking. In the absence of complete proof, many are willing to conclude that allergy or hypersensitivity is the underlying basis for the collagen diseases, and some even

include in this group syndromes in which there is allergy or presumed allergy even when the alterations in collagen tissue may be minimal or not evident. Obviously, present evidence does not justify these assumptions.

Great interest has been aroused by the discovery that patients with chronic rheumatoid arthritis are strikingly benefited by the parenteral administration of cortisone (17-hydroxy-11-dehydrocorticosterone) or of adrenocorticotropic hormone (ACTH). There also is meager evidence to suggest that patients with acute rheumatic fever and with disseminated lupus erythematosus may be helped by this therapy. It is possible that this observation will lead to an understanding of the mechanism whereby lesions occur in collagen tissue, and it may also strengthen the clinical and experimental evidence which suggests that a common or related etiologic factor is present in the various disorders now included under the term collagen disease.

The four diseases under consideration in the present chapter—namely, polyarteritis nodosa,

disseminated lupus erythematosus, scleroderma, and dermatomyositis—possess certain common and other dissimilar clinical features. Thus Raynaud's phenomena may occur in all of them. Except possibly in dermatomyositis, arthralgia and arthritis are common findings. Erythematous and purpuric skin lesions may be observed in any one of them. Visceral lesions, particularly cardiac involvement, have been demonstrated frequently in each of the four. Renal involvement is found frequently in polyarteritis nodosa and in disseminated lupus erythematosus. Pulmonary lesions and lesions of serous membranes may be present in all these diseases except, perhaps, dermatomyositis. A comparison of the symptomatology of these disorders is presented in table 43. Because of the varied and inconstant manifestations of each, it is difficult occasionally to separate one from another of these disorders, especially early in the course of the illness. At times any one of these diseases is accompanied by manifestations which closely resemble those of rheumatic fever or rheumatoid arthritis.

Table 43

COMPARISON OF CLINICAL CHARACTERISTICS OF POLYARTERITIS NODOSA, DISSEMINATED LUPUS ERYTHEMATOSUS, SCLERODERMA, AND DERMATOMYOSITIS

Clinical Characteristics	Polyarteritis Nodosa	Disseminated Lupus Erythematosus	Scleroderma	Dermatomyositis
Sex incidence: M:F.....	4:1	1:3.5	1:1	1:1
Commonly noted age of onset (in years).....	20-40	15-40	30-50	10-50
Arthralgia or arthritis (relative frequency)*.....	++	++	+	±
Cutaneous lesions.....	++	+++	+++	++
Cardiac involvement.....	++	++	±	±
Hypertension.....	++	±	-	-
Pulmonary lesions.....	+	+	±	-
Pleuritis with or without effusion.....	±	++	-	-
Abdominal pain.....	++	+	-	-
Impaired renal function.....	++	+	-	-
Lymph node enlargement.....	+	++	±	±
Splenomegaly.....	±	+	-	-
Peripheral neuritis.....	++	+	±	±
Focal brain lesions.....	+	±	-	-
Muscle inflammation.....	+	±	±	+++
Abnormal laboratory findings:				
Anemia.....	+	++	±	±
Leucocyte count (usual).....	Elevated	Reduced	Normal	Normal
Eosinophilia.....	+	±	±	+
Abnormal urinary sediment.....	++	+++	±	±

\* Frequency roughly estimated as follows:

+++ = 60-100%

++ = 40-59%

+ = 20-39%

± = less than 20%

- = a frequency no greater than in the ordinary population of the same age

### POLYARTERITIS NODOSA (PERIARTERITIS NODOSA)

**Definition.** This is a systemic disease, chronic or subacute in its course and frequently fatal, which is characterized by lesions of medium-sized arteries and arterioles of erratic and inconstant distribution. Variable visceral lesions and diversified clinical manifestations are the result.

**Synonyms or Allied Affections.** Periarteritis nodosa, disseminated necrotizing vascularitis, generalized arteritis.

**Etiology.** In experimental animals such as the rabbit and rat, single or repeated intravenous injections of heterologous serum (e.g., horse serum) or serum protein fractions may lead to a widespread arteritis similar to that encountered in human subjects with this disorder. In these animals, similar vascular lesions may develop following production of hypertension through reduction of renal blood flow by various procedures. In humans, the pathologic and clinical picture of polyarteritis has been observed in instances of serum sickness and in certain types of drug sensitivity, especially sensitivity to sulfonamides. In many clinical cases of polyarteritis nodosa, however, there is no history obtainable of any type of allergy either to drugs or to foreign proteins. Since the pathologic picture of arteritis from varied causes may be identical, it is impossible to state with certainty that all human cases of polyarteritis represent the result of a hypersensitivity reaction. Various infectious agents (viruses, bacteria, *Rickettsia*) have been suspected as etiologic factors without proof.

**Incidence.** Approximately 500 cases of this disease have been reported. Undoubtedly many others have occurred. The ages of affected individuals have ranged from 3 months to 87 years, but the highest incidence is between 20 and 40 years of age. The ratio of affected males to females is variously stated as being 3:1 or 4:1.

**Pathology.** This disease primarily affects medium-sized and small arteries and arterioles. Large arteries may be involved through lesions of the vasa vasorum. Rarely the veins are affected. Gross anatomic findings are variable and may be meager or absent. Small yellow or red aneurysms may be noted in mesenteric arteries or in arteries of various viscera. More often, one detects only visceral lesions resulting from ischemia or hemorrhage. Lymph node enlargement, splenomegaly, and serous effusions occur occasionally.

Histologically, the characteristic lesions are found in small and medium-sized arteries and in arterioles. Often only short segments of a vessel are affected. The entire circumference of the vessel or only a portion of it may be involved. The distribution of vascular lesions from case to case varies considerably. In approximately decreasing frequency, lesions of vessels are observed in the kidney, heart, liver, gastrointestinal tract, mesenteric vessels, spleen, pancreas, lung, muscles, and peripheral nerves. Almost any organ and tissue of the body may be affected.

The earliest lesion consists of necrosis and fibrinoid change in the inner portion of the media. This process may spread to involve the entire vessel wall. With extension into the intima, thrombosis may occur. When the vessel wall is weakened, aneurysm may form, or rupture of the vessel may occur and hemorrhage take place. The acute degenerative or necrotizing phase is followed by leukocytic infiltration of the vessel wall. This usually begins about the vessel and extends toward the lumen. At first, polymorphonuclear leukocytes and sometimes large numbers of eosinophils comprise the exudate. Later, plasma cells and lymphocytes with variable numbers of eosinophils are present. Subsequently, fibroblastic proliferation occurs in and about the damaged vessel. Ultimately there may be healing of the lesion and the result may be a scarred vessel with a narrowed or obliterated lumen. Usually it is possible in a given case to demonstrate vessels in all stages of degeneration and repair. This is in keeping with the remittent clinical pattern which is so often observed. Occasionally, granulomatous lesions which cannot specifically be related to arterial lesions are present in the lungs and other viscera. A certain number of patients with renal vascular involvement develop severe hypertension which may lead to the production of arteriolar changes of a hyaline or necrotizing type.

**Clinical Picture.** This disorder has as diversified symptomatology as has syphilis, but unfortunately is not detectable by any serologic test as is the case with syphilis. Only by histologic examination of material obtained by biopsy or necropsy can a positive diagnosis be made.

The onset may be insidious or abrupt. In a relatively small number of cases, hypersensitivity to serum or to a drug initiates the process. In a

few others, the symptoms appear during convalescence from an infectious process, much as is the case with acute rheumatic fever following a sore throat. In most cases, however, no predisposing factor is apparent. Recently acquired bronchial asthma, cutaneous eruptions, severe abdominal pain, cardiac failure, arthralgia or arthritis, myalgia, or peripheral neuritis are only a few of the presenting symptoms or findings which may be observed in these patients.

As the disease progresses, almost any region of the body may be affected. Frequently it is the multiplicity of superficial and visceral lesions which suggests the diagnosis. Often, also, the remittent character of the lesions is a striking feature. ~~A variety of cutaneous eruptions~~ may be observed. Purpuric lesions, erythematous eruptions of the type described as erythema nodosum or erythema multiforme, and lesions showing focal necrosis suggesting embolic manifestations may be encountered. There may be subcutaneous nodules. Many of the patients present themselves primarily as having ~~neurologic disorders~~. Subjective paresthesias, sensory impairment, muscle tenderness, and muscle wasting suggest the presence of peripheral neuritis. Headaches, convulsions, papilledema, and cranial nerve palsies may be confused with cranial neoplasms. Muscle tenderness may appear even in the absence of peripheral neuritis. This may be attributable to extensive inflammatory changes in the muscles. Painful joints which may or may not be swollen and tender are observed often. Retinal hemorrhages and exudates may be noted.

The ~~cardiovascular system~~ frequently is implicated. At least half of the patients develop hypertension during the illness. Pericardial friction rubs, cardiac enlargement, and tachycardia out of proportion to existent fever or anemia may call attention to heart injury. Systolic murmurs are noted frequently but diastolic murmurs are unusual unless concurrent or previous rheumatic infection has ensued. Electrocardiographic evidence of heart injury may be obtained. A few patients develop cold hypersensitivity of the Raynaud type.

A number of patients develop ~~asthma~~ during their illness. Less frequently, cough, hemoptysis, and pulmonary infiltrations are observed. The first evidence of pulmonary infiltration may be obtained from single or from serial x-ray studies. Pleuritic pain may occur.

Evidence of ~~gastrointestinal involvement~~ may be manifest by the occurrence of nausea, vomiting, diarrhea, or melena. Frequently, there is severe abdominal pain which may lead to exploration for suspected appendicitis or cholecystitis. Histologic inspection of inflamed tissue removed at the time of operation may disclose the necrotizing arteritis characteristic of this disorder. Occasionally, there is diffuse liver injury with or without jaundice.

Renal injury is observed in a relatively large proportion of cases. Gross hematuria may occur. More often, symptoms and signs of impaired renal function are observed. Not infrequently this may lead to uremia. Hypertension usually is present when renal damage is marked.

During the course of the disease, intermittent fever frequently occurs. The height of the fever and its type are varied. Loss of weight and of strength often are striking.

Death results most often from renal injury with concomitant hypertension, or from heart failure due to extensive myocardial damage. A great variety of other types of visceral lesions may lead to death, however.

**Laboratory Data.** A slight to moderate normocytic anemia is a common finding. The leukocyte count characteristically is elevated, ranging from 12,000 to 50,000 per cu. mm. Very occasionally there is leukopenia. When the leukocyte count is normal or increased, the differential count usually discloses an increase in polymorphonuclear leukocytes. In about one fourth of the cases, a marked eosinophilia is observed in a random examination. When repeated differential counts are made, eosinophilia, often transient, is found in a greater number of cases. Urine examination often discloses the presence of albumin, casts, red corpuscles, and white blood cells, even in the absence of impairment of renal function. Spinal fluid examination is usually normal, even in the presence of peripheral neuritis or central nervous involvement. A moderate hypoalbuminemia and slight hyperglobulinemia are common findings. Other laboratory abnormalities vary, depending on the extent and type of visceral damage. False positive serologic tests for syphilis are rare in this disease.

**Diagnosis.** It is usually impossible to make a certain diagnosis in the absence of histologic evidence of arteritis. Perhaps most characteristic is the changing clinical picture with evidence of

involvement of many tissues or organs. The intermittent and remittent course also is helpful. From a laboratory standpoint, leukocytosis, eosinophilia, and urinary abnormalities are suggestive. Approximately one fourth of cases are recognized clinically, the remainder being disclosed at necropsy. When the disease is suspected, biopsies should be made if the lesions are in the skin, subcutaneous tissues, or muscle. Since the vascular involvement is so patchy, a negative biopsy does not exclude the diagnosis.

The rare disorder, temporal arteritis, provides an interesting contrast to polyarteritis nodosa. In both diseases, the histologic changes in the arteries are somewhat similar. However, in temporal arteritis (cranial arteritis), unlike polyarteritis nodosa, the process involves large arteries and is, in the main, confined to the vessels of cranial distribution. (See description of temporal arteritis in Chapter 2.)

**Prognosis.** The difficulty in recognizing this disorder by clinical means impedes accurate prognosis. Of those cases diagnosed during life, recovery occurs in approximately one half, or at least remissions of several years' duration take place. When death occurs, this ensues usually within two years after the onset of symptoms. The prognosis is distinctly more grave in patients with clinical evidence of cardiac or renal involvement.

**Therapy.** At the present time there is no specific therapy. Appropriate supportive measures are indicated. Evaluation of any therapeutic measure is difficult because of the frequent occurrence of spontaneous remissions.

### DISSEMINATED LUPUS ERYTHEMATOSUS

**Definition.** Disseminated lupus erythematosus is a chronic, often remittent but usually ultimately fatal, disorder in which a peculiar skin eruption is accompanied by marked constitutional symptoms and variable visceral manifestations. In occasional cases, no cutaneous lesions develop. Certain variants of this disorder have been termed Libman-Sacks disease (atypical verrucous endocarditis) and the Senechal-Usher syndrome.

**Incidence.** About 80 to 85 per cent of reported cases have occurred in females, most commonly between the ages of 15 and 40 years.

**Etiology.** The cause is not known. Frequently the earliest symptoms appear after intense exposure to sunlight. In other instances, infections and trauma of various sorts appear to initiate the process.

**Pathology.** In autopsied cases, gross findings often are slight and may be absent. Frequently there is the characteristic cutaneous eruption. Many times there is focal or diffuse involvement of serous membranes (pleura, pericardium, peritoneum, joints) characterized by thickening with or without effusions. Moderate splenomegaly and focal or diffuse lymph node enlargement may be encountered. Verrucous, small and large non-bacterial endocardial lesions involving heart valves and the adjacent mural endocardium are present in some cases. Hemorrhagic and indurated lesions may be found in various supporting tissues and in the viscera. Frequently, the anatomic changes are complicated by terminal bacterial infectious processes. About 20 per cent of cases are found to have focal active tuberculous lymph node involvement.

Histologically, a variety of lesions have been observed, many of which may be absent in a given case. Primarily the changes occur in collagenous connective tissue and consist of both proliferative and degenerative lesions of fibroblasts and of collagen substance with varying degrees of leukocytic infiltration. Most characteristic, but not specific for this disease, is the so-called fibrinoid degeneration in which collagen assumes an amorphous appearance, staining intensely eosinophilic with the ordinary hematoxylin-eosin stain. The blood vessels may be extensively or sparsely involved in this process. In capillaries, small arteries and occasionally in venules (both systemic and pulmonary), there may be proliferative intimal changes, sometimes with thrombi, degenerative changes in the media and variable degrees (usually sparse) of leukocytic infiltration. Extravasations of serum and erythrocytes may appear about capillaries which appear dilated but otherwise normal. Connective tissue changes of the type described above may be present in serous membranes and supporting tissues. In the heart, even in the absence of gross endocardial lesions, there may be subendothelial collagen necrosis, leukocytic infiltration, and proliferation and degeneration of overlying endothelial cells. Focal myocardial changes may be

present. The spleen and lymph nodes may show cellular hyperplasia with or without foetal areas of cellular necrosis. A frequent finding is the presence of loose concentric rings of collagen about the small arteries in the spleen (periarterial fibrosis). In the kidney, glomerular lesions are observed frequently and changes may be present also in tubules and in renal vessels. There may be foetal proliferative and degenerative changes of glomerular epithelial and endothelial cells with occasional thrombi in capillary loops. More characteristic but not entirely specific for this disease is the occurrence of focal, irregular thickening of the capillary basement membrane within the glomerulus—the so-called wire loop lesion. The bone marrow may be normal or hypoplastic. Areas of hemorrhage and softening may be present within the nervous system. It is claimed that histologic sections from typical skin lesions present a characteristic appearance, judged not by any one microscopic change but rather by a specific combination of histologic changes.

To the pathologist, apart from the skin eruption, the occurrence of serous membrane involvement, endocardial lesions of the type described, periarterial fibrosis in the spleen, wire loop lesions in the glomeruli, and fibrinoid changes of collagen in vessels, would support the diagnosis of disseminated lupus erythematosus. The specificity of any one of these lesions for this disease seems improbable. Fatal cases have occurred in which none of the visceral lesions described could be demonstrated.

**Clinical Picture.** Like the pathologic changes, the clinical manifestations of this disorder are extremely varied. Early symptoms frequently noted are fever, arthralgia and arthritis, pleuritic pain, loss of weight, dyspnea, and orthopnea. The skin eruption which is so useful in establishing the diagnosis may have preceded the systemic symptoms for years, may appear early or late in the illness, and may be present transiently or may persist. As the disease progresses, evidence of constitutional symptoms such as fever, tachycardia, anorexia and loss of weight usually develops. Variable manifestations of peripheral and visceral involvement appear and then may disappear permanently or transiently. The general course of the illness is downward. There are more and more constitutional symptoms and evidence

of ever increasing visceral involvement. The tendency for remissions and exacerbations is very pronounced, however.

~~X~~The characteristic skin lesion is an erythematous eruption which sooner or later involves the malar region and the bridge of the nose, the so-called butterfly distribution. The lesions are raised and indurated and have sharp margins. The surfaces often present silvery scales which, when scraped away, reveal dilated follicles. Older lesions may show central atrophy. Similar lesions may be present elsewhere on the body. The skin eruptions usually are symptomless. It should be emphasized that lesions of similar appearance, which are histologically indistinguishable, may be present in otherwise normal individuals for years and never be associated with systemic manifestations (chronic discoid lupus erythematosus). Rarely, systemic lesions develop in such individuals years after the appearance of the skin lesions.

The Senechal-Usher syndrome is regarded as a variant of disseminated lupus erythematosus. In this disorder, erythematous scaly lesions of the face and neck are found in conjunction with bullous lesions of the rest of the body. The lesions, apart from those on the face, simulate those of pemphigus vulgaris.

In addition, many other types of skin lesions may be encountered, such as areas of telangiectasia, pigmentation (foetal or diffuse), purpuric lesions, petechiae with central pallor, ecchymoses, hemorrhages, indurated nodules in the finger tips (sometimes crusted), urticaria, lesions of the type described as erythema multiforme, and patchy areas of alopecia. ~~X~~

Nearly all patients develop joint symptoms. There may be only a migratory arthralgia. Frequently there is tenderness and swelling of several joints. Redness of overlying skin is rare. Bony deformity is an unusual manifestation. Joint involvement may be migratory, transient, or persistent. Frequently it is intermittent.

Edema is another common finding. This may be periorbital, dependent, diffuse, or focal in character.

Most patients complain from time to time of pleuritic pain. Pleural involvement may be evidenced by a friction rub or an effusion. Peritoneal rubs may be heard from time to time. Presumably as the result of serous membrane involvement of the peritoneum, focal or diffuse

abdominal pain may occur. Nausea, vomiting, anorexia, occasionally diarrhea may be present. Objective abdominal findings are rare. In a small number of cases, the spleen is moderately enlarged and palpable.

**X** Cardiovascular symptoms occur frequently and usually are characterized by dyspnea, sometimes by manifestations of failure. Cardiac involvement may be evidenced by a pericardial friction rub, tachycardia out of proportion to fever and anemia, cardiac enlargement, gallop rhythm, and rarely by manifestations of a pericardial effusion. Systolic murmurs are found frequently; however, diastolic murmurs seldom are present. The presence of diastolic murmurs should suggest an associated rheumatic valvular lesion; diastolic murmurs also could occur when there is a complicating bacterial endocarditis, when there is very extensive pulmonary involvement producing a Graham Steell murmur, or when anemia is very marked. Petechial cutaneous lesions with pale central areas may occur in association with or in the absence of nonbacterial verrucous endocarditis. When a true bacterial endocarditis supervenes, petechiae also may occur. A few patients give a history of cold hypersensitivity, usually of the Raynaud type.

Other manifestations may occur and give rise to signs or symptoms. Lesions of mucous membranes may be noted. Hemorrhages and exudates may be present in the retina. There may be symptoms of reduced renal function. Late in the illness, true uremia occurs rarely. Evidence of pulmonary or hepatic involvement and of endocrine disturbances has been described. Amenorrhea is frequently present. The central nervous system may be affected, giving rise to many manifestations, of which the most common are headache, delirium, and coarse tremors of the extremities. Late in the illness superimposed infectious processes occur frequently, particularly bronchopneumonia.

There are no characteristic roentgenographic changes. Such studies, however, may be helpful by revealing visceral involvement such as cardiac enlargement, pleural and pericardial effusions, pulmonary infiltration, and splenomegaly. Usually the affected joints show no changes other than soft tissue swelling.

**Laboratory Data.** Examination of the blood usually reveals a normocytic anemia. This may be severe. The leukocyte count characteristically

is low (2000 to 4000 per cu. mm.), but may be normal or elevated. In a given patient, the leukocyte count, determined repeatedly, may show wide variations. There is no characteristic alteration in the differential count. The platelets may be reduced in number and in certain instances this may account, in part at least, for an observed hemorrhagic diathesis. Generally, the erythrocyte sedimentation rate is elevated markedly. Stained smears of aspirated sternal marrow may disclose occasional large polymorphonuclear leukocytes in the cytoplasm of which large nuclear fragments in varying stages of digestion may be found, the so-called "L.E." cell. The specificity of this cell for this disorder and its frequency of occurrence have not been determined. The total serum protein is usually normal but the serum albumin is reduced and the globulin increased, thus giving rise to a reversal of the albumin-globulin ratio. Electrophoretic studies have disclosed the globulin elevation to be due largely to an increase in the gamma-globulin fraction. False positive flocculation and complement-fixation tests for syphilis or anticomplementary Wassermann tests are found in nearly one fourth of the cases. These changes may be intermittent.

The urine often contains albumin, usually in small amounts. The urinary sediment may show red corpuscles, white cells, and casts in the presence or absence of clinical evidence of impairment of renal function. Frequently, red blood corpuscle casts, fatty and waxy casts, and oval fat bodies are found simultaneously in the urinary sediment. This combination of urinary casts is unusual in other forms of nephritis. Laboratory evidence of moderate reduction in renal function is found frequently. Occasionally, renal function may be impaired severely.

Electrocardiographic changes of nonspecific character may be present in patients with or without demonstrable clinical cardiac involvement.

**Clinical Course.** The chronicity and remittent character of the disease have been emphasized. Nearly all patients in whom the diagnosis could be established with reasonable certainty have died. Usually death has occurred within one to two years after the diagnosis has been made. In retrospect, however, many patients are found to have had symptoms compatible with the disease for a period of two to five years prior to its recognition. Death may occur from a superimposed

infection (pneumonia, bacterial endocarditis, septicemia), from cardiac failure, or from uremia, or may follow ill-defined symptoms.

**Diagnosis.** This disorder is uncommon. Diagnosis is easy after the appearance of the characteristic skin eruption. In its absence, however, the recognition of the disease may be extremely difficult. The occurrence of arthritis, fever, loss of weight, pleuritis, cardiae and renal involvement, and anemia and leukopenia in a woman of child-bearing age should lead one to suspect the diagnosis. Often it can be established only after prolonged observation of the patient. In the occasional case in which the characteristic skin eruption never appears, the diagnosis is difficult to make with assurance, although it may be strongly suspected. The term Libman-Sacks disease is applied to cases studied anatomically in which a nonbacterial endocarditis is associated with other visceral lesions commonly found in disseminated lupus erythematosus. In many, but not all, of these cases a rash characteristic of this disease has been observed.

**Differential Diagnosis.** Because of the variability of the manifestations of this disorder, it may simulate many diseases. At times it may be impossible, at certain stages, to differentiate it from other members of the so-called collagen diseases. Often the bizarre symptoms with the paucity of findings lead to a diagnosis of psychoneurosis. Rheumatoid arthritis, Felty's syndrome, rheumatic fever, subacute bacterial endocarditis, erythema nodosum and erythema multiforme, brucellosis, tuberculous infections, systemic fungous diseases, sarcoidosis, lymphomas, and aleukemic leukemia are only a few of the conditions which may be confused with disseminated lupus erythematosus.

**Treatment.** Therapy is nonspecific. The variety of therapeutic measures advocated attests to their inefficacy. The parenteral administration of heavy metals (bismuth, gold), sulfonamides and antibiotics, roentgen therapy, nitrogen mustards, vaccines, vitamins, castration, and a variety of hormone preparations have been tried. None of these measures can be recommended as effective. The use of certain of these agents has been followed by aggravation of symptoms. Exposure of the skin to direct sunlight should be avoided, as this has been found to stimulate the disease in many instances. During periods of moderate or slight activity of the disease, physical exertion

should be restricted. Therapy otherwise should be supportive. Adequate nutrition and rest, transfusions for severe anemia, and suitable antibiotics for the treatment of complicating bacterial infections are advised. Sulfonamide therapy should be avoided unless no other measure will control an existing infection. A superimposed sulfonamide sensitization might aggravate the underlying disease. Some symptomatic relief may be afforded in certain cases by the administration of moderate doses of salicylates and related compounds. Occasionally, narcotics must be employed to provide comfort for the patient.

## SCLERODERMA

**Definition.** Scleroderma is a disorder characterized pathologically by an alteration in collagen tissue and clinically by focal or diffuse induration of the skin. There may or may not be associated vasomotor disturbances, evidences of visceral involvement, and endocrine manifestations.

**Etiology.** The etiology is unknown. Endocrine, vasomotor, and neurotrophic factors and hypersensitivity have been suggested. This is a relatively uncommon disease, more frequent in women, which occurs most often between the ages of 30 and 50 years.

**Pathology.** In the skin there is atrophy of the epidermis with flattening of the dermal papillae and often atrophy of the dermal appendages. Fragmentation of elastic tissue in the corium occurs frequently. The corium appears more dense than usual due to swelling, proliferation, and fusion of collagen fibrils. Small arteries of the corium may have thickened walls and narrowed lumens. Early, there may be edema and a moderate mononuclear cell infiltration in the corium. Late, exudate is less evident. Calcification may ensue. Similar changes in collagen tissue may be present in muscle fascia, in muscle itself, and in various viscera, especially the heart, lungs, and gastrointestinal tract. Frequently, the histologic alteration appears less striking than the change in consistency of involved tissue.

**Clinical Types.** The disease exists in a focal form in which indurated cutaneous lesions are found on the trunk, neck, or extremities. At times these lesions follow the distribution of peripheral nerves. Apart from its cosmetic effects, the focal form seldom has significance, since it progresses to the more diffuse type only rarely. The more diffuse form of scleroderma often is accompanied

by constitutional symptoms. There are two types of the diffuse form. *Diffuse scleroderma* commonly begins with induration of the face, neck, and proximal portions of the upper extremities. Ultimately, this may involve much of the skin of the body. In this type, vasomotor disturbances, at least in the early stage, are infrequent. A second type, known as *acrosclerosis*, usually is associated with vasomotor disturbances at the onset, and there is early involvement of the distal portions of the upper extremities and of the face. This form is more prone to be accompanied by visceral lesions in the late stages. Many cases, however, do not fall readily into either of these groups.

**Clinical Pictures.** The onset often is insidious. Early symptoms frequently noted include slight fever, edema which may be focal or diffuse, arthralgia, and mild arthritis. Many patients give a history of vasomotor disturbances, particularly of the Raynaud type, for months or years preceding the changes in the skin.

As the disease progresses, conspicuous changes are found in the skin, especially of the face, neck, and upper extremities. The severity of the process in different parts of the body may vary greatly. The involved skin has a waxy sheen, is taut, and cannot be lifted from the underlying structures. In the affected areas of skin, pigmentation, depigmentation, loss of hair, and telangiectasia are often noted. Occasionally, there may be severe cyanosis. Erythema may occur. When the face is involved, the features may assume a masklike appearance and there may be limitation of the movements of the jaw. Induration of the skin of the extremities and girdle regions may give rise to limited motion and contractures. Atrophy of underlying muscle is likely to occur. Deformities of the fingernails may be observed. Trophic ulcerations may develop in any involved area, and paresthesias and reduction in sensory perception may be present. Indurated lesions may be found in the mouth and may affect the tongue and gums. Dysphagia may result from diffuse induration of the esophagus with impaired peristaltic motility, or may be the consequence of stenosis of the lower portion of the esophagus, an esophageal hiatus hernia, or cardiospasm. Involvement of the heart may lead to impaired function of this organ. Implication of the lungs with pulmonary insufficiency has been noted rarely. Dyspnea in this disease may

be due to pulmonary or cardiac lesions or to impaired excursion of the abdomen and thorax due to thickening of the skin. Constitutional symptoms usually are mild. A low-grade remittent fever may be noted. Loss of weight may be slight or marked. Associated endocrine disturbances may be present, although their varied nature makes it appear that they do not constitute an integral part of the disease. There may be thyroid, pancreatic islet, pituitary, and even adrenal functional disturbances without these endocrine structures showing any pathologic lesions characteristic of scleroderma.

**Laboratory Data.** Significant deviations of formed elements of the blood from the normal range seldom occur. A slight anemia and moderate increase in the erythrocyte sedimentation rate may be noted. Urinary abnormalities are infrequent. The basal metabolic rate usually is within the normal range. Calcium, phosphorus, and other blood constituents usually are normal. A significant reduction in serum albumin associated with a moderate elevation in total serum globulin is found occasionally. Slight spontaneous creatinuria (100 to 300 mg. per 24 hours) is a frequent finding in adults. However, marked creatinuria is rare. Suitable temperature studies may elicit the characteristic vasomotor disturbances of Raynaud's syndrome. Roentgenograms may show areas of osteoporosis and destructive lesions of the bone of the terminal phalanges. Likewise, involvement of the esophagus, lung, and perhaps the heart, may be disclosed by radiographic techniques. Abnormal electrocardiograms may be found in those with cardiac involvement. Biopsy of the affected skin may disclose the characteristic pathologic lesion.

**Clinical Course.** The course of this disease is extremely varied. The extensive changes in the skin may lead to severe contractures and to partial or complete invalidism. Food intake may be difficult because of limited movement of the jaws as a result of thickening of the overlying skin of the face or because of dysphagia from esophageal changes. Trophic ulcerations occur frequently in areas where the skin is indurated. The disease may at any point in the course regress spontaneously or become stationary. Death attributable specifically to cardiac or pulmonary sclerodermatous lesions rarely results. More commonly, death occurs from an intercurrent infection in a patient debilitated by this disorder. The mor-

tality rate is not high, ranging from 10 to 20 per cent.

**Diagnosis.** In the advanced case, the characteristic skin induration makes easy the recognition of this disorder. Early, the occurrence of edema, arthralgia, and vasomotor disturbances (Raynaud phenomena) should lead to consideration of this disease. Focal and diffuse scleroderma may be encountered in the condition of dermatomyositis, which is recognized primarily by the associated muscle tenderness. One disorder, scleroderma adultorum (scleriasis), may be impossible to distinguish from scleroderma at an early stage. This usually appears, one to six weeks following an upper respiratory infection, as a brawny induration involving the neck and trunk. The hands and feet rarely are affected. After an indefinite period, usually less than six months, this induration disappears entirely.

**Treatment.** There is no specific treatment. Cervicodorsal sympathectomy has given symptomatic benefit in selected cases with pronounced vasomotor disturbances, but usually has not resulted in the regression of lesions. In those patients with very low basal metabolic rates, administration of desiccated thyroid has produced improvement occasionally. Other therapeutic measures have included thyroidectomy, parathyroidectomy, administration of parathormone, large doses of vitamin D or neostigmine, iontophoresis with methacholine chloride, and fever therapy. Success has not been impressive. The judicious use of physiotherapy to prevent and overcome contractures and to maintain and improve muscle strength seems to be the most reasonable form of treatment at this time. For those patients with vasomotor disturbances, avoidance of exposure to cold and meticulous care of the hands to prevent trauma and infection are indicated. In those with extensive skin involvement but without vasomotor disturbances, trauma must be avoided. Large doses of paraaminobenzoic acid have been found to be helpful in a few cases. Also, in a small series of cases, testosterone propionate with or without small amounts of added estrogen has appeared to be beneficial.

### DERMATOMYOSITIS

Dermatomyositis is a chronic and often fatal disorder affecting primarily the skin and striated muscle. The etiology is unknown. Depending in

part upon the character of the manifestations, other names have been applied to this disease. These include *polymyositis*, *dermatomyositis*, *neuromyositis*, and *poikilodermatomyositis*.

This disease is uncommon. It has been observed in whites, Negroes, and Orientals. Individuals of any age may be affected, but it is most frequent between 10 and 50 years. There is no sex predominance.

**Pathology.** Gross anatomic findings usually are meager and may be absent. One may detect changes in striated muscles, a cutaneous eruption, and occasionally lymph node and splenic enlargement. The histologic changes observed in involved skin are not characteristic. The microscopic findings in the muscle may be diffuse or focal in distribution. Sometimes they are confined to a segment of a given muscle. The muscle fibers themselves show considerable proliferation of sarcolemmal nuclei. Occasionally, there are large giant cells, thought by some to be of muscle origin. The muscle fibers may show atrophy, necrosis, loss of striation, hyalinization, fragmentation, or fatty and waxy degeneration. Occasional fibers may be undergoing phagocytosis. A slight to moderate infiltration with lymphocytes and histiocytes may be present in interstitial tissue which frequently is increased in amount. In the small arteries and arterioles the wall may be thickened and the lumens narrowed.

Rarely, changes similar to those occurring in skeletal muscle may be present in the myocardium. Perineural cellular infiltrations have been observed.

**Clinical Picture.** The onset usually is insidious. Not infrequently a recent upper respiratory infection precedes the earliest symptoms. Patchy erythema or edema, myalgia, or vasomotor disturbances may be presenting symptoms. Often periorbital edema is an early complaint.

The skin manifestations are extremely diverse and are not specific. Most common are erythematous eruptions. Purpuric, vesicular, and desquamative lesions have also been described. Particularly in those patients in whom there is a history of Raynaud's phenomena, but even in some without such a history, there may be sclerodermatosus involvement of fingers, hands, forearms, and face. Occasionally this is diffuse. In areas of thickened skin, there may occur pigmentation, trophic ulcers, and slight sensory impairment. Apart from the sclerodermatosus

lesions, pigmentation, depigmentation, telangiectasia, and alopecia may be noted. Occasionally there is increased sweating.

Subcutaneous edema of the face, trunk, or extremities is not infrequent. There may be erythema of the overlying skin. Periorbital edema occurs in many patients.

Most characteristic is the evidence of muscle involvement. Frequently, the patients complain of stiffness, tenderness, decreased strength, and easy fatigability of the affected muscles. This may be focal or diffuse at the onset. As the disease progresses, skeletal muscles of the trunk and proximal portions of the extremities tend to show the greatest involvement. The consistency of the affected muscles is variable. Usually, one may elicit tenderness by pressure and passive motion. Atrophy, contractures, and even calcification of muscles may be present.

Apart from skeletal muscle, the striated muscles of the eyes, pharynx, larynx, and diaphragm, and the intercostal muscles are affected frequently. This may give rise to such symptoms as diplopia, dysphagia, hoarseness, and dyspnea. Rarely, the heart muscle is implicated, with resultant cardiac insufficiency.

In occasional cases one may encounter other manifestations such as tongue and mucous membrane lesions, retinal changes, lymph node enlargement, splenomegaly, mild neurologic disturbances, hemorrhagic tendencies, and arthralgia.

Patients with dermatomyositis frequently lose considerable amounts of weight. However, other constitutional symptoms are usually slight. Fever is present in less than half of the patients, usually is mild when it occurs, and tends to be intermittent. Marked tachycardia in the absence of cardiac involvement is infrequent.

**Laboratory Findings.** A slight anemia is noted frequently. The leukocyte count is usually normal. In about 30 per cent of patients, an increase in eosinophils or monocytes, or both, is found in the differential count. Usually the erythrocyte sedimentation rate is increased moderately. There may be a reduction in serum albumin and an increase in serum globulin. Proteinuria has been observed in some cases, but other evidence of renal damage is uncommon. In some cases with cardiac involvement, electrocardiographic changes have been noted. By fluoroscopy, or indirectly by vital capacity measurements, it may

be possible to demonstrate reduced expansion of the thoracic cage and reduced excursion of the diaphragm with respiration. Occasionally, osteoporosis is found by roentgenography. The spinal fluid is normal.

¶ A relatively constant finding in adults is the reduction in urinary excretion of creatinine per 24 hours in association with a spontaneous creatinuria which may range from 200 to 1200 mg. per 24 hours. Moderate daily fluctuations in creatine excretion occur, and marked variations may be found as the disease alters in severity. Creatinuria, which occurs normally in children and may occur in healthy women, especially prior to menstruation, is increased beyond physiologic amounts in dermatomyositis.

The histologic changes found in biopsies of affected muscles in dermatomyositis are not distinguishable from the changes in muscle in a number of other disorders. Hence an abnormal muscle biopsy alone does not suffice for a positive diagnosis.

**Clinical Course.** There is a tendency for remissions and exacerbations to occur. There may be spontaneous complete recovery, or the individual may be partially or completely incapacitated by muscle atrophy, contractures, and weakness. The fatality rate in large series has been found to be 50 to 60 per cent, death usually occurring within two years after the establishment of the diagnosis. The illness may, however, have been present for a number of years prior to recognition. Death usually results from intercurrent infections, particularly pneumonia. In patients with severe involvement of the diaphragm and intercostal muscles, death may be due to respiratory paralysis. Less commonly, death occurs from cardiac involvement with ensuing heart failure. The prognosis is stated to be somewhat better in children than in adults, particularly in the older age groups.

**Diagnosis.** The diagnosis is made readily in an advanced case. Early, it may be impossible to recognize this disorder. The presence of muscle tenderness and muscle atrophy in conjunction with periorbital edema should suggest the diagnosis. Laboratory findings which may assist in the diagnosis are decreased urinary creatinine excretion together with spontaneous creatinuria, an increase in monocytes and eosinophils in the stained blood smear, and biopsy evidence of muscle involvement.

**Differential Diagnosis.** Early, psychoneurosis and psychogenic rheumatism may be suspected. As the disease progresses, the possibilities for consideration become very numerous. They include polyarteritis nodosa, disseminated lupus erythematosus, thyrotoxic myopathy, peripheral neuritis, progressive muscular atrophy, myasthenia gravis, myositis ossificans, trichinosis, sarcoidosis, pellagra, thromboangiitis obliterans, and even Addison's disease. Since sclerodermatos changes may appear in dermatomyositis, it may be difficult or impossible to differentiate between dermatomyositis and scleroderma unless extensive muscle involvement is present. A number of observers consider these two disorders to be variants of a single process. Others believe the two to be distinct diseases.

**Treatment.** There is no satisfactory treatment. Measures employed include fever therapy, physiotherapy, administration of vitamin E, treatment with heavy metals, and oxygen inhalation. In the writer's experience, restricted activity during periods of exacerbation, application of moist heat, appropriate physiotherapy, and encouragement to the patient have yielded moderate benefit. Oxygen therapy and even a respirator may be needed where respiratory distress is marked. Salicylates in small or moderate doses seldom give relief of symptoms. Occasionally, large doses bring dramatic relief, but the attending symptoms of salicylate intoxication may be worse than the disease.

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## 39

### Disorders of the Joints

Max Michael, Jr.

Introduction  
 Anatomy and Physiology of Articular Structures  
 Approach to the Patient with Joint Disease  
 Classification  
 Rheumatoid Arthritis  
 Degenerative Joint Disease  
 Polyarthritis and Fever  
 Trauma and Joint Disease  
 Psychogenic Rheumatism  
 Palindromic Rheumatism  
 Reiter's Syndrome

### INTRODUCTION

The ancient, somewhat ambiguous term *rheumatism* is frequently applied to diseases, both acute and chronic, which are characterized by pain and stiffness of muscles, joints, and neighboring structures. *Arthritis*, denoting inflammation of joints, is used more commonly. This term, however, is not altogether correct since in many types of joint diseases inflammation is not present. In some diseases in this group, occasional aches and stiffness may be the only manifestation; in others, permanent and severe crippling deformities may ensue.

Symptoms referable to articular structures may be evoked by primary musculoskeletal disease (e.g., degenerative joint disease), by constitutional disease with predominance of phenomena related to the musculoskeletal system (e.g., rheumatoid arthritis), by constitutional disease with fleeting symptoms referable to the musculoskeletal system without appreciable outstanding structural change (e.g., meningococcemia), and by complaints of psychogenic origin with fixation on the musculoskeletal system (e.g., psychogenic rheumatism).

It has been estimated that disability from joint diseases has been responsible for the invalidism of 150,000 persons in the United States each year and that because of the long duration of rheumatic diseases, the total disability caused by them exceeds that due to tuberculosis by 10:1, that due to cancer by 7:1, and that due to diabetes by 10:1.

In this chapter attention is focused upon generalizations concerning joint disorders and upon entities of less well-understood etiology; where joint affections are produced by specific etiologic agents, they will be discussed elsewhere in relation to the agents concerned.

### ANATOMY AND PHYSIOLOGY OF ARTICULAR STRUCTURES

Joints are admirably constructed to serve their functions of weight bearing and motion. The articular ends of bones are covered by resilient cartilage which is lubricated by synovial fluid. Apposed joint surfaces are so formed as to permit maximum useful motion for that particular joint. The knee, for example, permits only flexion and extension, while the ball-and-socket shoulder permits motions through a much wider range. A tough, inelastic connective tissue capsule encloses each joint space and blends with the perichondrium and periosteum. Tendons and ligaments inserting into the capsule contribute to its strength. Lining the capsule is a modified connective tissue, the *synovial membrane*, which is soft and freely movable. The membrane itself consists of a single layer of cuboidal cells which

are not separated from the surrounding areolar or fibrous tissue by a basement membrane. These synovial cells, best described as mesothelial, have been shown to produce in tissue culture a mucin-like substance. Loose connective tissue and areolar tissue lie beneath the synovial layer, forming the subsynovial tissue. Being richly supplied with blood vessels, nerves, and lymphatics, the membrane possesses good powers of repair and regeneration. Its fine folds and trabeculations provide a large surface area and permit considerable stretching. The synovial membrane extends for only a short distance onto the articular cartilage, leaving the articular surfaces in close apposition to one another. The membrane encloses tendon sheaths and in many areas forms the lining of bursal sacs.

*Articular cartilage* is avascular and depends upon synovial fluid for its nourishment. Its ability to recoil after compression enables it to withstand the wear and tear of weight bearing and motion. Its powers of regeneration are poor, and with advancing years certain degenerative changes begin to appear. They consist primarily of splitting and loss of normal architecture of the cartilage. The significance of these changes will become apparent when degenerative joint disease is considered.

*Synovial fluid*, a viscous, relatively acellular fluid, is present in varying amounts in joint spaces and is increased in volume in most diseases of the joints. The fluid lubricates the joint and furnishes nutrition to cartilage. In addition, it may provide bactericidal substances which may aid in protecting the joint against infection. The fluid in human beings normally contains about 60 cells per cu. mm. These are principally monocytes, lymphocytes, and tissue phagocytic cells. The chemical constituents of synovial fluid are such as to suggest that it is a dialysate of blood plasma with the addition of mucin. The protein content averages about 1.7 Gm. %, the albumin fraction predominating. The highly viscid nature of synovial fluid is due to the *mucin* normally present in amounts of from 0.3 to 0.8 Gm. per 100 ml. Chemical examinations indicate that mucin is a protein-polysaccharide complex, similar to the mucoprotein of connective tissue intercellular substances. Through its osmotic effects mucin aids in the transfer of water between plasma and synovial fluid and is apparently the important factor in the lubri-

cation of joints. It also protects cartilage from friction of motion.

It has been demonstrated that penicillin diffuses freely into joint spaces and that detectable levels persist longer there than in the plasma. This is an important consideration in the use of this antibiotic for infected joints.

**Joint Pain.** Anatomic studies have demonstrated a rich network of nonmyelinated fibers following the course of arterioles and supplying the synovia, subsynovial tissues, joint capsule, tendons, periosteum, and adjacent muscles. Articular cartilage and compact bone are insensitive to painful stimuli. The nerves supplying articular and periarticular structures are branches of the dorsal root nerve supplying that area.

Unpleasant sensations in joints range from mild, transitory aches and stiffness to severe, exericiating pain requiring opiates for relief. Joint pain is variously described as "throbbing," "boring," "squeezing," "aching," and "burning." The same sensation is experienced in a joint when sensitive structures are stimulated, be it by a pinch, tear, cut, stick, or chemical irritant. Pain may be appreciated only locally, as in the joints of the fingers, or may be referred to distant areas as, for example, the pain in the knee which may accompany pathologic changes in the hip. Moreover, pain arising around the joint may be sensed as pain in the joint. Spasm of muscles adjacent to joints further adds to pain appreciated in those joints by the stimulation of nerve endings in the periosteum at the sites of tendon attachment to the bones.

#### APPROACH TO THE PATIENT WITH JOINT DISEASE

An optimistic attitude on the part of the patient and, more important, on the part of the physician could do much to diminish the incidence of invalidism attributable to joint disease. The good physician approaches the patient with "rheumatic" complaints with an alert mind, seeking to classify specifically the type of disease, to discover cause and precipitating factors where possible, and to use intelligently and enthusiastically the tools of physical medicine, psychotherapy, chemotherapy, dietotherapy, and general medical therapeutic aids.

A careful, complete history and physical examination should be carried out on all patients. Details as to onset of pain, type and duration of

pain, and history of similar episodes must be recorded. Notes should be made of objective joint findings and should include degree of heat, redness, swelling, deformities, and range of motion. Such observations serve as an index of progress at subsequent examinations. A battery of "routine" laboratory tests is not essential and, by the same token, routine x-rays may be omitted in many cases.

Cytologic, chemical, and bacteriologic examinations of *synovial fluid* will often yield information of considerable diagnostic and prognostic value. For culture, a few drops of the aspirated fluid should be inoculated directly at the bedside onto a warm chocolate agar plate. The heavy inoculum is often necessary in order to demonstrate gonococci. Organisms of the pleuropneumonia group can also be isolated on this medium. For cell counts, 2 ml. of freshly drawn synovial fluid is placed in a tube containing 0.1 mg. of potassium oxalate; 0.1 ml. of this fluid is diluted in the white cell pipet with 0.9 ml. of physiological saline to which a trace of gentian violet has been added. Total and differential counts may then be carried out in the counting chamber. If only a few drops of tissue juices are obtained, it is helpful to use this material for culture and cell count. Upon the addition of acetic acid, mucin precipitates as aropy clot in normal and traumatic effusions. In septic and rheumatoid effusions the clot is poor and the solution turbid. With improvement in the disease the clot becomes firmer. As indicated in table 44, there is considerable variation in values in any group of

patients with the same type of joint disease. The findings in synovial fluid must be interpreted in the light of the clinical features observed.

It is to be emphasized that the great majority of patients suffering from rheumatic disorders are the victims of a chronic disease. The physician must not become impatient because marked improvement is not noted over the course of a few days. In most instances, many months, even years, of close observation and care of the patient are needed for the proper management of his problem. Long-continued observation will aid the physician in his approach to the problem and will serve as a psychotherapeutic aid to the patient.

## CLASSIFICATION

It is convenient to have a working classification of joint diseases. The following outline is recommended by the American Rheumatism Association and appears in the "Standard Nomenclature of Disease and Operations." At present it seems to be the most satisfactory.

1. Arthritis due to specific infection. Specify organism when known.
2. Arthritis due to rheumatic fever.
3. Arthritis, rheumatoid. Specify as multiple or of spine.
4. Degenerative joint disease, multiple due to unknown cause; osteoarthritis.
5. Arthritis due to direct trauma.
6. Arthritis due to gout.
7. Neurogenic arthropathy.

Table 44  
SYNOVIAL FLUID FINDINGS IN VARIOUS JOINT AFFECTIONS\*

Condition	Leukocytes		Polymorphonuclears		Mucin Clot
	Minimum	Maximum	Minimum	Maximum	
Normal.....	..	65	..	6	Good
Rheumatoid arthritis.....	500	230,000	3	97	Poor; improves as joint subsides
Gonococcal arthritis.....	1600	250,000	50	100	Poor
Rheumatic fever.....	1000	50,000	2	98	Good
Tuberculosis.....	500	100,000	2	80	Poor
Reiter's syndrome.....	1000	35,000	25	90	.....
Traumatic arthritis.....	50	8,000	2	90	Good
Gout.....	1000	70,000	0	99	Poor

\*Figures represent composite of those of many authors. (Although the wide overlap is evident, such examinations are of considerable diagnostic and prognostic value.)

8. New growths of joints.
9. Hydrarthrosis, intermittent.
10. Periarticular fibrosis.
11. Diseases in which arthritis, arthropathy, or arthralgia are frequently associated (diagnose disease, list joint manifestation as symptom):

Acromegaly	Ochronosis
Acute disseminated lupus erythematosus	Osteochondritis dissecans
Cyst of meniscus of knee	Osteochondromatosis
Dermatomyositis	Periarteritis nodosa
Drug intoxication (Specify)	Psoriasis
Erythema multi-forme exudativum	Pulmonary osteo-arthropathy
Erythema nodosum	Purpura, various types
Hemophilia	Raynaud's disease
Hysteria	Reiter's disease
	Scleroderma
	Serum sickness

### RHEUMATOID ARTHRITIS

**Definition.** Rheumatoid arthritis (atrophic arthritis; chronic proliferative arthritis; arthritis deformans) is a systemic disease in which inflammatory changes in articular and periarticular structures predominate. These changes may progress to fibrous, and later to bony, ankylosis of joints with resulting characteristic deformities. Chronicity with spontaneous remissions and exacerbations are noteworthy features. In addition to changes in the joints, there may be lesions involving practically every system of the body.

**Etiology.** Although the precise etiology of rheumatoid arthritis is unknown, certain recently discovered facts concerning the relationship between adrenal cortical hormones and rheumatoid arthritis afford leads toward solution of the problem. The following concepts of etiology are discussed not only for historical reasons but because they may tie in with the newer ideas on etiology.

A vast amount of investigative work has centered around attempts to isolate *specific infectious agents* from the synovial fluid, synovial tissues, lymph nodes, or blood of patients with rheumatoid arthritis. The occasionally reported isolation of *beta-hemolytic streptococci* or of nonhemolytic streptococci from such patients has not been corroborated. All attempts to isolate viruses have been fruitless.

The elevated serum titer of agglutinins against the beta-hemolytic streptococcus occurring after the first year of the disease in a high percentage of patients has suggested to many investigators the causative role of this organism. More recent work has shown, however, that these agglutinins are, in all probability, nonspecific and represent some abnormality in the serum proteins of these patients. The theory that a hidden *focus of infection*, such as an infected gallbladder or a chronic prostatitis, not only caused but actually influenced the course of rheumatoid arthritis enjoyed wide popularity for a number of years. More careful evaluation of patients after the removal of such suspected foci has led most workers to abandon any idea that such foci are concerned with the pathogenesis of the disease. *Psychogenic factors* can influence the course of the disease but do not appear to be directly concerned with its etiology. Emotional trauma apparently can precipitate a relapse, and may be responsible in some cases for continued activity. Rheumatoid arthritis, along with rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa, scleroderma, and dermatomyositis, is referred to as a "collagen disease." The allusion may be artificial, but lesions in connective tissue are common to all. Interest recently has centered around the chemical constituents of connective tissue and possible alterations of them in the collagen diseases. Briefly stated, the fibrous elements are denatured proteins of high molecular weight. The supporting ground substance is composed of protein mucopolysaccharide complexes. Of the four polysaccharides which have been recognized, chief interest at present is in the highly polymerized hyaluronic acid. Hyaluronic acid appears in increased amounts in the synovial fluid of patients with rheumatoid arthritis. It exists in an incompletely polymerized form, and thus the fluid is less viscous than normal. Since the enzyme hyaluronidase, which is capable of de-polymerizing hyaluronate, has not been demonstrated in synovial fluid or in periarticular tissues, it has been suggested that the defect lies in the faulty synthesis of hyaluronate by connective tissue cells. It should be mentioned that the "spreading effect" of hyaluronidase is inhibited by cortisone. Increasing evidence demonstrates that these protein-polysaccharide complexes are concerned with the etiology of rheumatoid ar-

thritis in a manner as yet not completely understood. Many features have suggested that rheumatoid arthritis belongs to the group of diseases that are evoked by an *immune mechanism*. This postulates an antigen-antibody reaction taking place in and on involved tissues and resulting in the alterations noted. The histologic changes have features in common with those in others of the collagen group of diseases (Chapter 38). Were such a hypothesis to be proved correct, it would probably be demonstrated that a number of different antigens are capable of altering the synovial tissue—or perhaps all of the so-called collagen tissues.

It has been known for some time that remissions in rheumatoid arthritis occur when patients become either jaundiced or pregnant. A common denominator, "antirheumatic substance X" was suggested. Preliminary studies on patients who have received cortisone (17-hydroxy-11-dehydrocorticosterone, compound E), one of the adrenal cortical hormones, have indicated that this compound is in some fashion concerned with the etiology of rheumatoid arthritis. In the limited number of patients with active rheumatoid arthritis who have received cortisone, improvement has been dramatic. The elevated sedimentation rate returns to normal, at times after only five days of medication. The articular pain, swelling, and stiffness rapidly subside and the defects in plasma proteins and hemoglobin quickly revert toward normal. Improvement is transitory in that the disease flares up immediately upon withdrawal of cortisone. Similar effects have been noted upon administration of pituitary adrenocorticotrophic hormone (ACTH). There is no overt evidence of adrenal insufficiency in patients with rheumatoid arthritis. Furthermore, the amount of cortisone needed daily to maintain remissions far exceeds that needed for the treatment of Addison's disease—a true adrenal insufficiency. Cortisone, therefore, probably plays a direct pharmacologic role rather than one of correcting a deficiency. Realizing the control of the adrenal cortex over all body metabolism, it becomes difficult to rationalize completely this newly observed fact with the exact etiology of rheumatoid arthritis. The principal promise of this discovery is that a new approach is provided—one which may ultimately solve the puzzle. Finally, it is possible that rheumatoid arthritis is not a specific entity but rather a

*nonspecific process* which may result from several different stimuli.

**Pathology.** The changes in *articular structures* are a consequence of synovial proliferation, destruction of cartilage, resorption of bone, and ankylosis. The early changes consist of lymphocytic infiltration in subsynovial and synovial tissue, edema, and hyperemia. The infiltration is diffuse at first but later coalesces, forming dense lymphocytic nodules throughout involved areas. Adjacent tendons are often involved by the inflammatory process. As the disease progresses, the synovial membrane proliferates and spreads across the articular surface as granulation tissue, called pannus. The proliferation occurs from all sides of the joint and tends to grow across the joint surfaces. As the pannus grows, it extends into and destroys cartilage by interfering with its nutrition. Accompanying this may be the production of granulation tissue on the marrow side of the subchondral bone plate, the latter being invaded and cartilage destroyed. Hence, destruction of cartilage may take place from two sides. The tendency of the pannus to unite the articular surfaces by a bridge of granulation tissue may lead to fibrous ankylosis. Should perichondral proliferation be a prominent feature, bony ankylosis may ensue. The sequence from edema to pannus formation and fibrosis does not take place in all instances. Remissions of the disease may occur at any stage, but residual articular and periarticular thickening will usually be found. Accompanying the changes in the synovial membrane are alterations in the joint capsule. These consist principally of thickening of the entire capsule, which, at the periphery of the joint, is continuous with the process in the synovial membrane. Such capsular thickening contributes to restricted joint mobility.

Some correlation between clinical and pathologic findings can be made. Joint swelling can be attributed to capsular thickening and effusion into joints, the latter being more important where large joints are involved. Bone resorption is explicable on the basis of disuse and invasion of the epiphyseal bone plate by granulation tissue. Joint dislocation may result from distortion of the joint space, from interruption of bone remodeling sequences, and from the pull of muscles in spasm. All of the changes mentioned may be found in a single joint. When cartilage has been eroded and fibrous ankylosis has developed, the

changes are irreversible. Most, if not all, of the joints involved in the rheumatoid process eventually demonstrate many of the histologic lesions of degenerative joint disease (see p. 489).

It is important to note that *visceral lesions* are associated with the changes in the joints. *Muscle lesions* may be observed in patients with rheumatoid arthritis. These consist of lymphocytic infiltrates, frequently in clusters, which form nodules between muscle fibers and about blood vessels. Varying degrees of muscle degeneration may be noted. Lesions may be found not only in close association with involved joints but also in muscles remote from them. It should be pointed out that somewhat similar lesions have been found in muscles of patients with other diseases, but they are far more frequent and more extensive in rheumatoid arthritis.

No specific lesion has been demonstrated in the *brain* and *spinal cord*, though the alterations in the cord usually attributed to aging are more common in patients with this disease than in other persons of the same age. In approximately 85 per cent of patients examined there are small collections of mononuclear cells within the nerve sheaths, usually the perineurium, of the peripheral nerves. The axons and myelin sheaths often show changes along with corresponding anterior horn cell degeneration. These findings may explain the paresthesias and twitchings often noted.

*Subcutaneous nodules* are found over tendon sheaths and bursae and in subcutaneous tissues. Less commonly, nodules develop in the myocardium and larynx. These consist of clusters of granulomatous lesions which contain a central necrotic zone of an eosinophilic staining material and which are surrounded by a palisade of swollen fibroblasts and sparse lymphocytic infiltration. Sequestrums of collagen may persist in the central necrotic core. This structure differs from the subcutaneous nodules of rheumatic fever in that there is no marked inflammatory reaction and the edema of collagen is not observed. This, perhaps, explains the longer duration of the rheumatoid nodules as compared with the more ephemeral ones of rheumatic fever.

Various studies of the *heart* at autopsy have reported lesions, said to be indistinguishable from those of rheumatic fever, to be present in from 26 to 66 per cent of cases of rheumatoid arthritis. These consist of gross lesions of valves and pericardium and of Aschoff bodies in the valves,

myocardium, and pericardium. An occasional aortitis and aortic valvulitis has been noted. The incidence of such changes is apparently higher than that observed in controls, and raises the question whether rheumatoid arthritis and rheumatic fever are closely related diseases or whether the findings are merely coincidental. Other studies have shown that these minor changes occur in control hearts of nonrheumatoid patients. (Careful clinical evaluation of the heart in patients with rheumatoid arthritis has failed to reveal an appreciable percentage with murmurs, enlargement, or other evidence of cardiac disease.) Evidence of pericarditis has been reported in autopsy findings.

Glomerular endothelial proliferations have been noted. Hyperplasia of endothelial cells may result in moderate lymph node hypertrophy. The nodes often contain an amyloid hyalin. Amyloidosis is found in 25 to 30 per cent of patients with rheumatoid arthritis. The occurrence of this entity in chronic infections is well known, but its true incidence and significance in rheumatoid arthritis is not well explained.

**Pathologic Physiology.** Certain alterations in body physiology occur in patients with rheumatoid arthritis. *Plasma proteins* in patients with severe disease may demonstrate depression of serum albumin to quite low levels, while the globulins become elevated. Electrophoretic studies have shown that early in the disease alpha-globulins are elevated, whereas later the gamma-globulins predominate. A similar pattern has been noted in the synovial fluid, except that the concentration of gamma-globulins may be higher than in the serum. Disturbances of *calcium metabolism* have been thought by many to play a prominent role in rheumatoid arthritis. Since balance studies, however, have shown nothing more than a slight increase in urinary calcium excretion, it is probable that calcium metabolism is essentially normal. *Peripheral vascular system:* The cold, moist extremities common in this disease suggest that circulation in the extremities is altered. Measurements have shown some increase in vascular tone in the smaller vessels of the hands and feet. These may explain the Raynaud-like symptoms that are noted. Extensive studies of the *gastrointestinal tract* have shown no consistent aberrations from normal. Alterations in liver function have been reported, but most of the changes are those which would

be associated with abnormalities of protein metabolism. The rare finding of gynecomastia suggests faulty detoxification of estrogens, presumably by the liver.

**Epidemiologic and Environmental Factors.** The onset of rheumatoid arthritis occurs most frequently in the third and fourth decades. However, it has been observed to begin in children under one year of age and in patients in the ninth decade. Women are more often affected than men by a ratio of 3:1. A family history of similar deformities is occasionally obtained. Such could be the result of common environmental factors. Respiratory infections, sore throats, and surgical procedures may apparently precipitate an attack.

The temperate zones and, in particular, those areas with damp, cold climate have the highest incidence of rheumatoid arthritis. It is common belief that episodes of cold, damp weather can aggravate the symptoms of the disease. More exact studies have demonstrated that the weather prognostication of patients with arthritis is actually quite faulty, and that patients vary from day to day in their response to changes in weather. The "bad days" associated with cold, damp weather or with change in barometric pressure may be related to emotional letdown that most individuals experience with such climatic conditions. Victims of rheumatoid arthritis fall into all social and economic strata. The incidence of the disease is higher, however, in the crowded, unhygienic conditions of the lower economic groups. No type of body build is free from the disease. The belief that the thin, asthenic individual is more apt to be stricken has not been entirely corroborated by recent anthropometric studies.

While perhaps not directly concerned with the etiology of rheumatoid arthritis, the emotional patterns of patients, in all likelihood, play a prominent part in the subsequent course of their disease. Relapses are frequently preceded by periods of tension and anxiety. The patient with rheumatoid arthritis is apt to be an outwardly placid and calm individual, but beneath this placidity may lie a multitude of conflicts. The arthritis may serve as an emotional and physical "crutch." These patients frequently seem to lack the will and desire to "go the whole way" toward maximal relief of symptoms and may discontinue a regimen of therapy which is having a good effect.

**Clinical Features.** Rheumatoid arthritis is a disease of many and diverse clinical syndromes. It runs the gamut from an acute, febrile illness with rapid onset of deformities to one in which the only manifestation may be the accidental finding of rather characteristic deformities, the patient never having been aware of joint pain. However, this latter circumstance is rare.

Fatigue, lassitude, anorexia, and weight loss are frequently the earliest symptoms noted. Not uncommonly, emotional trauma, exposure to cold, surgical operations, respiratory infection, or fatigue are precursors of these prodromes. Numbness and paresthesias of the extremities are frequent complaints. These vague symptoms may be present for months before attention is called to the joints. Associated with the systemic symptoms are fleeting aches and pains in various muscles and joints; there may be a sense of stiffness toward the end of the day when the patient has become fatigued. At this stage of the disease the diagnosis of psychoneurosis is often made. It is to be emphasized, however, that the diagnosis, though difficult, may be suspected early when the vague symptomatology, without objective findings, is presented. Frequently, however, the patient does not consult the physician until deformities have developed. After weeks or months of such vague symptomatology, joint swellings may become obvious. The knees and proximal interphalangeal joints of the hands are apt to be particularly painful at this stage. Though any joint in the body may be involved, those most often affected, in addition to the above mentioned, are wrists, metacarpophalangeals of hands and feet, hips, sternoclaviculars, temporomandibulars, and ankles. The spine may be involved. This is to be distinguished from true rheumatoid spondylitis in which nodules do not occur and in which involvement of fingers occurs rarely. Other distinguishing features will be discussed later (see p. 487). Not infrequently a history of an episode of transitory joint pains which occurred many years previously is uncovered.

Patients at this stage may demonstrate many characteristic features of the disease. The palms and soles are moist and cold. Weight loss is usually evident. Generalized lymph node enlargement and splenomegaly may be noted although the latter is unusual. The hands present the typical findings of early rheumatoid arthritis.

Involvement of the articular structures of the proximal interphalangeal joints results in fusiform swelling of the fingers which is nearly pathognomonic of rheumatoid arthritis. One or all fingers may be involved, and the process is bilateral in the majority of cases. At this stage the fingers tend to be partially flexed; full flexion and extension are limited by pain, muscle spasm, and effusion into joint spaces. Flexion at the metacarpophalangeal joints, with the added tendency to ulnar deviation, imparts the "flipper-like" appearance to the hand. The early onset of interosseous muscle atrophy is striking. Other joints, particularly the knees, may be swollen. The skin over the joint may be warm. An early and striking finding is muscle atrophy, most prominent around severely involved joints. Particularly rapid in development is atrophy of the quadriceps groups, this being responsible for the extreme weakness of the legs. Low-grade fever with daily swings to 100° F. may occur.

Rheumatoid arthritis is characterized by remissions and relapses. A complete or partial remission may occur at any stage of the disease. Striking remission of symptoms may occur during pregnancy or when the patient is jaundiced. These remissions may now possibly be correlated with the newer knowledge of cortisone. It is conceivable that this hormone is not excreted by the liver of the patient with hepatitis and that it is produced in excess by the gravid patient or by the fetus. Although the remission may be complete or of many years' duration, in the majority of cases symptoms recur at frequent intervals, and progression continues until the disease is finally inactive or "burned out." Activity, on the other hand, may continue and the process advance in relentless fashion. Continuing articular disease and the adjacent muscle spasm may cause severe deformities. The types of deformity that will ensue in a given joint are predicated to a large extent on gravity and on the pull of adjacent muscles; in general, flexors are more powerful than are extensors, and hence the appearance of flexion deformities. The hands may assume ulnar deviation and flexion at metacarpophalangeal and wrist joints; the knees and elbows may be held in a flexed position. If the patient takes to his bed, he finds it more comfortable to place a pillow under his knees, favoring flexion contractures, and to lie with the shoulders adducted and the elbows flexed, favor-

ing contractures in these positions. Continuing disease destroys articular cartilage; further deformities, subluxations, and even eventual bony ankylosis may take place. In neglected cases the end stages of irreversible contractures, subluxation, and ankylosis result.

Certain *associated features* offer some aid in diagnosis, in estimation of prognosis, and in evaluation of extent and severity. Subcutaneous nodules appear in about 20 per cent of patients with rheumatoid arthritis. They are firm, round or ovoid, nontender masses which vary from 2 to 3 mm. to 2 to 3 cm. in diameter. They are present singly or in clusters. The overlying skin is movable. A frequent site of involvement is the olecranon bursa, which may contain a cluster of nodules. A large nodule may develop on the extensor surface of the forearm 2 to 3 inches below the elbow. Other areas of involvement include tendon sheaths of the fingers, the Achilles tendon, around the wrist, over the patella, scalp, scapula, spinous process, and sacrum. The nodules in general are most common during the active stages of disease and portend a poorer prognosis. Unlike the nodules of rheumatic fever, which may be quite transient, they usually persist for months or years.

*Ocular manifestations* are interesting and unexplained. *Uveitis*, with burning, lacrimation, and photophobia, is reported in from 0.6 to 4.7 per cent of cases. Panophthalmitis and cataract formation may occur. When of long duration, it may lead to a thick, dry band of corneal opacity, the so-called *keratite en bandelette*. Episcleritis which is usually bilateral is also noted in some cases. It does not disturb vision but may invade the edge of the cornea. A rare but serious affection frequently resulting in loss of the involved eye is *scleromalacia perforans*. In this condition nodules form in the sclera with perforation and extrusion of contents of the bulb.

The *skin* of the extremities, particularly the hands and soles, is clammy. Over the hands and feet and often over the extremities it is atrophic and shiny. Transient erythematous macular rashes on the trunk, face, and forearm may be observed. A bronze discoloration is often present over the face, neck, chest, and extremities. Erythema of the hypothenar eminence, the so-called "liver-palms," is frequently present. Rarely a purpuric eruption develops over the shins. Other rare manifestations which serve to emphasize the

systemic nature of rheumatoid arthritis include pleurisy with effusion, pericarditis, and myocarditis. Bilateral Dupuytren's contractures may be seen.

The *varied clinical manifestations* which may characterize rheumatoid arthritis can cause diagnostic problems. It is difficult to conclude with any certainty that a given episode of joint pain is, or is not, rheumatoid arthritis. An acute onset with chills, a septic type of temperature swinging as high as 105° F., pleuritis, peritonitis, pericarditis, and transient rashes may resemble rheumatic fever. The joint pains may be minimal early in such an episode. In many such patients only time reveals the true nature of the disease, when the characteristic joint changes of rheumatoid arthritis then become evident. Acute gout may be marked by such an onset. Although the arthritis is most often polyarticular and symmetric, rheumatoid arthritis may be manifested by swelling and pain in a single joint. Such is the case in about 10 per cent of patients. This may persist as monarticular arthritis for years until the more typical variety, with involvement of interphalangeal and other joints, makes its appearance and clarifies the otherwise unexplained monarticular disease. In some cases, swelling in one or more bursae, particularly the olecranon, may be the earliest manifestation of the disease and may precede the development of joint changes by many months. Another form responsible for confusion is that which masquerades as myositis or fibrositis with soreness and stiffness of muscles for years. The following types of atypical onset and course of rheumatoid arthritis have been described: (1) A sudden febrile onset following an acute infection, accompanied by skin rash and migratory joint involvement with localization in a few joints. (2) Sudden onset of joint symptoms and exquisite pain and tenderness in involved joints suggesting specific bacterial arthritis. This type of onset is often noted in patients over 50. (3) Acute febrile onset simulating acute rheumatic fever. (4) Predominately asymmetric joint involvement, frequently a monarticular disease. (5) Multiple recurrent attacks of pain and swelling, so-called "palindromic rheumatism." (6) Recurrent muscle aches and pains with little objective joint changes.

**Diagnosis.** This may be quite simple in the patient presenting the classic features of prodromal symptoms, paresthesias, weight loss, sym-

metric involvement of joints, remissions and relapses, and the fusiform swelling of the fingers. Where these features are not present, however, as in patients with the acute febrile polyarticular or with the monarticular varieties of the disease, then the diagnosis may be quite difficult. Careful evaluation of the clinical features and the laboratory findings often lend assistance, but in many instances only the passage of time reveals the true nature of the disease.

Among the entities that may mimic acute rheumatoid arthritis quite closely are rheumatic fever, gout, and gonococcal arthritis. The erythematous rash, acute polyarticular involvement, high temperature, and leukocytosis of acute rheumatoid arthritis may be easily confused with *rheumatic fever*, particularly in children. Development of murmurs and electrocardiographic changes, prompt response to salicylates (though occasionally it is as dramatic in rheumatoid arthritis), and freedom from joint changes between attacks favor a diagnosis of rheumatic fever. Histologic study of nodules may aid in differentiating the two diseases. *Gout*, with its periodic attacks, frequent involvement of the great toe, completely asymptomatic intervals between attacks, elevated serum uric acid, tophi, and response to colchicine, should not offer too much difficulty in diagnosis. It is to be remembered that gout may at times assume an acute polyarticular form with few, if any, remissions and a rapid onset of deformities which closely simulate those of rheumatoid arthritis. *Gonococcal arthritis*, particularly the type with noninfected fluid (see p. 834), may at times simulate rheumatoid arthritis. Isolation of gonococci from infected foci, response to penicillin therapy, and changing titer of the complement-fixation test fortify a diagnosis of gonococcal arthritis. *Disseminated lupus erythematosus* is often confused with rheumatoid arthritis, particularly in its early stages of migratory joint pains, fever, and weight loss. With the passage of weeks, involvement of the skin, kidneys, pleura, lungs, and heart provides a clearer characterization of the syndrome. Any disease entity or syndrome that is accompanied at some time or other during its course by migratory joint pains may be confused with rheumatoid arthritis. And, by the same token, acute rheumatoid arthritis is often confused with rheumatic fever, disseminated lupus, gout, gonococcal arthritis,

and many other conditions. During its incipient stage of arthralgias and constitutional symptoms and before objective joint pains are detected, rheumatoid arthritis is easily mistaken for *fibrositis*, an entity much more commonly diagnosed in Great Britain than in this country. It is also in this stage of the disease that rheumatoid arthritis is most easily confused with psychogenic rheumatism. *Degenerative joint disease*, to be discussed below, should offer little difficulty, but it is to be re-emphasized that in all cases of long-standing rheumatoid arthritis, pathologic changes of degenerative joint disease are present.

Of some but by no means of specific aid in the diagnosis of rheumatoid arthritis are certain *laboratory procedures*. *Anemia* is commonly present in cases of chronic rheumatoid arthritis. This is usually normocytic and normochromic, but may become microcytic. It has all the features of an anemia of infection. The white blood count is usually normal, but a leukocytosis of from 10,000 to 20,000 may be noted in acute cases. In children this may be as high as 50,000 per cu. mm. A corresponding increase in immature polymorphonuclear leukocytes is noted. In long-standing chronic cases a leukopenia as low as 1500 per cu. mm. may occur. The *sedimentation rate* is elevated in over 90 per cent of patients with active rheumatoid arthritis. It tends to return toward normal as the disease becomes quiescent. *Agglutination of sensitized sheep erythrocytes* appears to have some value as a specific laboratory test. The phenomenon depends upon the fact that serums from patients with active rheumatoid arthritis will agglutinate sheep cells which have been sensitized with rabbit amboceptor in significantly higher dilutions than it will sheep cells that have not been sensitized. The *synovial fluid* is usually a turbid, yellow color. The cell count averages from 10,000 to 30,000 with polymorphonuclear leukocytes comprising 90 per cent of the total count.

*X-ray changes*, other than soft tissue swelling, are not seen in early cases. As the disease advances, bone atrophy, together with narrowing and irregularity of joint spaces, becomes apparent. "Punched out" areas in bone proximal to joint spaces may be present. In advanced cases, subluxation, marginal erosions, and complete obliteration of joint spaces may occur. None of these changes is specific and each may be en-

countered singly or in combination in other varieties of joint disease.

**Treatment.** An approach to the patient as a whole should be the guiding principle in the treatment of rheumatoid arthritis. To concentrate on the treatment of joints alone is an unpardonable omission. By the same token, the indiscriminate administration of parenteral therapy, while neglecting the joints, is to be condemned. Close coöperation between the internist, physiatrist, and orthopedist is desirable. Patience on the part of both doctor and patient is essential. The physician who treats rheumatoid arthritis properly must be prepared to rehabilitate his patients both physically and emotionally. Patients treated within the first year of the disease tend to improve more rapidly and to have a better ultimate outlook than those in whom treatment is delayed. This further emphasizes the need for prompt diagnosis and institution of a good regimen. When the value of any given form of therapy is assessed, it must be remembered that rheumatoid arthritis is a disease of spontaneous remissions, some of them even permanent. The many claims of cure attributed to various remedies do not take this fact into account. There is apparently no specific "cure" for rheumatoid arthritis. It is not feasible to list and to comment upon the many drugs that have been tried in the therapy of rheumatoid arthritis. An air of healthy skepticism is wise before accepting as a "cure" any new drug. When the disease has become stable or "burned out," the physician should help the patient in readjusting to his altered way of life and aid him in vocational rehabilitation.

**GENERAL MEASURES: REST.** Rest is one of the most effective tools in the management of rheumatoid arthritis. The exact amount of rest a given individual should receive cannot be determined by a rule. In general, as long as the disease is active the patient with rheumatoid arthritis should restrict his activities. In milder forms this may consist of 2 hours' rest in the afternoon, 10 hours' rest at night, and a curtailment of normal activities. Patients with acute, febrile disease and those with rapidly advancing deformities should be at complete bed rest. Upon subsidence of temperature and activity of the disease, they should be allowed to ambulate gradually. A rule of thumb to follow in regulating subsequent ambulation is that activity which

does not incite fatigue should be permitted. Under ideal circumstances, the patient with active rheumatoid arthritis should be treated in hospital for at least three or four weeks. During this time he can be started on his medical regimen and instructed in the measures of physical medicine that he and his family may carry out at home. Emotional rest is difficult to achieve, particularly in a patient besieged by a chronic disease which carries with it the threat of a crippling disability. However, it is the responsibility of the physician to obtain for his patient as complete emotional rest as possible. The first requisite for this is a sympathetic and understanding approach to the patient.

**DIET.** Most patients with rheumatoid arthritis are underweight, and attempts should be made to correct this. No foods should be restricted, and the older fads of restriction of citrus fruits, pork, and the like are to be condemned. No special diet is indicated other than one rich in proteins, calories, and iron, and adequate in the essential vitamins. Added calcium in the form of milk may aid in recalcification of bones. The practice of sending patients to *spas* is not so popular in this country as on the continent. No magical powers are possessed by the so-called healing waters, but rather it is probable that the change from home environment is responsible for the sense of well-being that the patients experience. Blood transfusions often seem to improve the sense of well-being of the patient with chronic rheumatoid arthritis. They should be given only when anemia is present.

**FEVER THERAPY.** At times, fever therapy such as that obtained with increasing amounts of intravenously administered typhoid vaccine will apparently hasten a remission. This measure, originally considered empiric, is worthy of trial in selected cases, especially those whose disease is stationary yet still active. It can be speculated that the chills serve as the stress for cortisone production, transient though it may be. Autogenous vaccines do not influence the disease in any other manner. The patient should make all attempts to avoid chilling by keeping involved joints well protected by warm clothing before subjecting them to the elements.

**RELIEF OF PAIN.** Much deformity can be prevented by using measures to relieve pain. Many of the physical measures to be mentioned are quite effective in alleviating pain. The proper use

of analgesics is one of the keystones of management. Salicylates in dosage as high as 0.9 Gm. every three hours may be required for relief of joint pain. Occasionally it may be necessary to combine codeine with the salicylates. Morphine, except in rare instances, should not be administered because of the danger of addiction. Sedatives are frequently of help, particularly in allowing the tense patient to rest well. It has been well demonstrated that bee venom and cobra venom have no place in the armamentarium for the relief of pain.

**THERAPY OF JOINTS.** All too frequently patients with advancing disease are treated with a multitude of injections of various sorts without the least attention being paid to their joints. This represents neglect. The prevention of deformities depends upon the judicious use of physical medicine, most measures of which are simple and can be carried out in the home. Rest of a joint is obtained by relief of weight bearing and by the judicious application of splints. For the wrists, a cock-up splint in the acute stages does much to prevent contractures. For the hands, a simple cuff of plaster incorporating the metacarpophalangeal and proximal interphalangeal joints will serve. For the knees, a bivalved cast extending from mid-leg to mid-thigh is needed. Splints should be removed three times a day, gentle massage given to the joints, and guarded, passive motion instituted to the point of pain. The activity has been too strenuous if pain persists for more than one hour after the exercise. Heat may be given to involved joints in the form of heat cradle, hot moist towels, paraffin baths, electric pad, or infrared lamp. Contrast baths are helpful to some patients. It is to be noted that all patients do not experience relief upon application of heat. Their pain may be intensified, as exemplified by those with acutely inflamed joints. Where many joints are involved, much relief is obtained by a hot tub soak once or twice a day, provided the patient is not debilitated. These procedures can be carried out by the patient or by his family at home. Procaine infiltration around acutely involved joints often produces dramatic temporary relief of pain. Administration of curare often relieves pain in a similar fashion by relaxing muscle spasm, particularly around large joints. During the relief of pain and spasm, a joint may be put through a wide range of motion and the vicious muscle

spasm-pain cycle broken up. The type of motion to be permitted a joint varies with the degree of activity of disease, but early attempts should be made to put all joints through as much motion as possible without producing pain which lasts more than one hour. It is to be emphasized that much of the residual weakness is due to atrophy of muscles adjacent to involved joints. This can be prevented or corrected, as the case may be, to a large measure by exercise aimed at developing the involved muscles. Those particularly apt to atrophy rapidly are the quadriceps when the disease is in the knee, and the extensors of the wrist when that joint is involved. Quadriceps "setting" exercises done 10 or 12 times each hour will do much to prevent atrophy. The patient can learn to contract this muscle group by pushing the knee backwards against the bed. Deformed joints are often helped by the judicious use of traction. There is not yet complete agreement as to the proper indications or time for surgical intervention in management of chronically affected joints. Such procedures as arthroplasty, fusion, synovectomy, all have a limited role. Frequent consultation with the orthopedic surgeon must be made before such procedures are to be recommended. Frequent examination of joints with recording of angles and degrees of joint motion is essential for judging results of therapy.

"SPECIFIC MEASURES." Many so-called specific measures have been introduced, but most are unsatisfactory. Although gold salts at present enjoy the widest popularity, results with these compounds are conflicting. Some writers report as high as 80 per cent relief of pain and shortening of the course of the disease. Others have shown that careful follow-up examinations have not demonstrated better results with the use of gold salts than with the use of general supportive measures. Gold is a toxic compound and is excreted slowly. Traces of the element may be found in the body as long as one year following the last injection. Toxic reactions such as agranulocytosis, thrombocytopenic purpura, exfoliative dermatitis, and nephritis have been reported. These may occur at any time during the course of therapy and, indeed, months after the regimen is stopped. The mortality rate from the use of gold is around 0.47 per cent. Should gold be used, its toxic properties must be carefully weighed against any possible benefit that

may be derived. Several compounds are available commercially; most are for intramuscular use. The most frequently used ones, with their percentage of gold, are as follows: Gold sodium thiosulfate ("Sanocrysin"), 37 per cent; gold sodium thiomalate ("Myoehrysine"), 50 per cent; gold calcium thiomalate (calcium aurothiomalate), 50 per cent; gold thioglucose ("Solganol-B Oleosum"), 50 per cent; gold thioglycolanilide ("Lauron"), 54 per cent. The last three are in oil suspension. A conservative regimen consists of an initial injection of 10 mg. of gold, followed by 25 mg. the second week, then 50 mg. a week from the third through the twenty-second week. A rest of one month is allowed, and then 50 mg. is given every three weeks for an indefinite period. Careful check of the skin, urine, and blood must be made before each injection, and at the first sign of toxicity the drug should be discontinued and BAL administered. There is evidence that BAL will diminish the toxic reactions. If gold is to be used, the more conservative measures of general medical care and physiotherapy must not be neglected. Massive doses of vitamin D compound ("Ertron") have also enjoyed wide use. Such drugs are to be condemned, as they not only do not influence the course of the disease but may lead to serious complications. Their property of raising the blood calcium level may lead to precipitation in the renal tubules, renal failure, and secondary hyperparathyroidism. Similarly, deficiency of vitamins is not at fault. A single vitamin concentrate tablet each day will more than compensate for any deficiency due to periods of anorexia and poor utilization. Chemotherapeutic agents, sulphonamides, penicillin, and streptomycin have no place in the treatment of rheumatoid arthritis per se. Neostigmine, sulfur compounds, antireticulocytotoxic serum, and spinal pumping similarly are without effect.

The striking and prompt improvement noted in the limited number of patients given cortisone warrants the statement that this hormone offers the greatest promise of any agent thus far used in rheumatoid arthritis. No previous type of therapy has induced a remission so completely and so rapidly. Too few patients have been treated to establish accurately the dosage, duration of treatment, and toxic effects. Similar effects have been obtained with ACTH. In most patients observed, relapse has occurred within a few days

after the drug was discontinued. It has been demonstrated that epinephrine can incite production of cortisone by the adrenal cortex indirectly through its stimulating effect on the anterior pituitary. Preliminary studies indicate that this method will not serve as a reasonable substitute for cortisone administration.

**Prognosis.** The ultimate outcome for a patient with rheumatoid arthritis depends upon many factors. Among these are the pattern his disease assumes, the vigor and promptness of his treatment, and the attention the physician gives to all matters relating to the disease.

Significant figures are reported in a series of 250 patients who had received simple medical and orthopedic measures and who were followed for an average of 10 years. Of these, 53.2 per cent were improved, including 15 per cent in remission; 12.8 per cent were stationary; and 34 per cent were worse. These figures correspond fairly closely to others reported in the literature. Features which indicated a better outcome of the disease were: asymmetric joint involvement; disease of less than 12 months' duration when treatment was begun; patients under 40 years; male patients; no marked weight loss; slight activity; and mild involvement. Relapses can be expected in approximately 30 per cent of patients; to predict them is difficult, but emotional and physical trauma, operations, and weight loss may hasten their onset. It has been estimated that in approximately 5 per cent of patients the disease pursues a relentless course with no remissions and with the rapid onset of deformities.

It has been said, and probably correctly so, that patients do not die of rheumatoid arthritis, but rather with it. Pulmonary complications such as atelectasis, infarctions, and pneumonia lead the causes of death in rheumatoid arthritis. Many of these, no doubt, result from the debilitated state of the far advanced cases. Sepsis, varying types of heart disease, and amyloidosis are other causes of death.

**Other Variants of Rheumatoid Arthritis.** It is generally believed that the following entities, though given varying names, represent forms of rheumatoid arthritis. Why they should differ in some respects from the classic variety of the disease is not clear.

**FELTY'S SYNDROME.** Five patients with rheumatoid arthritis, splenomegaly, yellowish brown pigmentation of the skin, and leukopenia were

described by Felty in 1924. It is apparent from further studies that this syndrome represents not a separate disease entity but rather a variant of rheumatoid arthritis. In many instances, careful search will reveal other causes for the leukopenia and splenomegaly. It is probable that hyperplasmia accounts for the leukopenia. There remains, however, the rare case presenting rheumatoid arthritis with splenomegaly and leukopenia. This descriptive terminology is to be preferred to "Felty's syndrome."

**STILL'S DISEASE** connotes rheumatoid arthritis in children. Distinguishing features include high fever, anemia, marked leukocytosis (even to 50,000) and generalized lymphadenopathy. Early in the course of the disease the differentiation from acute rheumatic fever may be quite difficult, but with progression and the onset of deformities, the diagnosis becomes obvious. Subcutaneous nodules are rare. Contrary to earlier beliefs, rheumatoid arthritis in children does not always assume a rapidly progressive course but may be quite mild, leaving minimal residual joint affections. In many cases, however, the disease is fulminating, with rapid onset of muscle wasting, demineralization of bone, contractures, and deformities. Amyloidosis is a common finding.

**PSORIATIC ARTHRITIS (ARTHROPATHIA PSORIATICA).** Psoriasis occurs in approximately 3 per cent of patients with rheumatoid arthritis. The incidence in comparable controls is of the order of 0.7 per cent. The psoriasis may have its onset before, concomitantly with, or after the appearance of joint changes. The nails are commonly involved, with scarring and pitting. Usually the skin lesions improve or regress with changes in status of the joint disease.

Involvement of the terminal interphalangeal joints is the most distinguishing feature of the syndrome. The pathologic changes are usually those associated with rheumatoid arthritis. In the rare reports of cases with exclusive involvement of the terminal interphalangeal joints, marked articular destruction, shortening of the middle phalanges, cuplike deformity of distal phalanges, and replacement of the joint space by dense, acellular fibrous tissue have been noted. Though the incidence of psoriasis is higher in rheumatoid arthritis than in the general population, it is nevertheless probable that the so-called psoriatic arthritis is not a specific entity but rather a variant.

RHEUMATOID Spondylitis (MARIE-STRUMPELL ARTHRITIS, ANKYLOSING Spondylitis, SPONDYLOSE RHIZOMELICA). Rheumatoid spondylitis is a chronic arthritis involving the spine and sacroiliac joints. In all likelihood it represents a variety of rheumatoid arthritis, but differs from it in several respects. Among these are its predominance in males, its propensity to produce calcification of ligaments, the absence of subcutaneous nodules, and its apparent good response to roentgen therapy. These differences justify separate consideration. (The occurrence ratio of spondylitis to rheumatoid arthritis of the peripheral joints is about 1:12, though, as might be expected, the experience in army hospitals indicated a ratio of 1:3.) In contrast to the peripheral type, 90 per cent of the cases of spondylitis occur in males. There is a tendency for several members of a family to be affected by spondylitis.

**PATHOLOGY.** The inflammatory process, a synovitis which is similar to that of peripheral rheumatoid arthritis, involves the posterior intervertebral joints, the only true diarthrodial joints in the spinal column. Later, calcification of the spinal ligaments occurs. Demineralization of vertebral bodies may be quite marked. Changes occur in the sacroiliac joints early in the course of the disease. These consist of condensation of bone on either side of the joint spaces with later narrowing and eventual obliteration of the articulations. Areas of patchy density may be noted in the pubes and ischia. Involvement of the hips and shoulders occurs in about one fourth of the cases. Pathologically, the lesions eventually show the changes of degenerative joint disease. Rheumatoid nodules may occur in patients with concomitant small joint involvement but have not been recorded in those with spondylitis alone.

**CLINICAL FEATURES.** Rheumatoid spondylitis begins insidiously in the majority of cases, usually between the ages of 20 and 40. Fleeting pains in the low back, some limitation of motion on forward bending, soreness in the buttocks, weight loss, and occasional sharp pains along the distribution of the sciatic nerve may be the earliest complaints. Low back strain or psychoneurosis are frequent labels given patients at this point. The only findings may be some restriction of forward bending with absence of lumbar lordosis and some tenderness to percus-

sion over the sacroiliac joints and the spinous processes. Low-grade fever may occur.

As the disease advances, involvement of other segments of the spinal column evokes varying clinical features. Pain may be quite severe. Spasm of the spinal muscles, which is a noteworthy feature, may cause kyphosis. With involvement of the costovertebral joints, the chest cage may lose its expansion, and pain may be experienced with deep respirations as well as on lateral compression of the bony thorax. Pain in the spine may be increased by sudden and violent movements and by sneezing and coughing. Root pains may be noted. Muscle wasting involving spinal, gluteal and thigh groups is frequent. The spine may be held erect as it fuses, producing the so-called poker spine. Often, however, the pull of spinal muscles causes flexion of the spine, and unless appropriate measures are taken, fusion will occur in that position. Remissions and relapses occur, but, in some cases, activity, characterized by continued pain and fixation, may be present constantly for 20 or more years. Finally, as the spine fuses, pain ceases. Cervical involvement limits neck motion. Rarely patients may be seen with the classical "poker spine" but without a history of significant pain in the past. Involvement of the hips, shoulders, and knees is not uncommon. Peripheral joints are involved in about 30 per cent of cases and may show the typical change of rheumatoid arthritis, but in about 50 per cent of these the peripheral joints may be expected to clear up. These changes may precede or follow the onset of spondylitis. Iritis occurs in approximately 25 per cent of the cases and may even precede spinal involvement. Repeated episodes of iritis may occur.

In a small group of patients, the onset is that of an acute, febrile illness with severe pain, anemia, and weight loss. This is easily confused with acute osteomyelitis.

**DIAGNOSIS.** Rheumatoid spondylitis is to be suspected in any young male with a backache. Limited motion of the spine with flattening of lumbar lordosis, diminished chest expansion, muscle spasm, and tenderness to spinal percussion are quite suggestive of the disease. Roentgenographic changes may not be noted during the first year of the process. Changes to be observed consist of fuzziness of the sacroiliac joints, spotty osteoporosis or osteosclerosis of bone adjacent to the articulation, and, finally,

complete fusion. Posterior intervertebral joint involvement shows up as fuzziness and joint destruction, with fusion at a later date. Oblique views of the spine are necessary to demonstrate these changes to an advantage. With advancing disease, the ligaments become calcified, producing the "bamboo spine." The sedimentation rate is elevated in approximately 80% of the cases and in general indicates the degree of activity. This is a most useful test in the differential diagnosis of backache in the young male. The spinal fluid protein is elevated in many cases, and in those with neurologic symptoms this may further confuse the picture. Anemia is often present.

**TREATMENT.** The aims of therapy are the relief of pain and fusion in the optimum posture. The general principles that guide the management of the patient with rheumatoid arthritis of peripheral joints apply to spondylitis. It is a systemic disease and should be managed as such.

During the acute phase, the patient should be in bed with a firm mattress for support. A board under the mattress is helpful. The pillow should be as low as possible—preferably, it should be omitted. To preserve normal lordosis, a small pillow should be placed under the lumbar spine for an hour three times a day. In severe cases, a plaster shell is indicated. Among the most important measures are deep breathing exercises carried out at regular intervals during the day. These will improve chest expansion and vital capacity and will strengthen the weakened respiratory and abdominal muscles.

Hot packs to the back three or more times a day do much to relieve the spinal muscle spasm and pain. Curare also relieves spasm, but its effects are transitory. The principles guiding the duration of bed rest are similar to those applicable to rheumatoid arthritis of the peripheral joints. Fatigue and increased pain are factors that should limit further increase in activity. With ambulation, strenuous efforts must be directed toward maintaining good posture and chest expansion. Remedial postural exercises, back braces, and continued use of deep-breathing exercises are all usually indicated.

Carefully controlled studies have demonstrated beneficial effects of x-ray therapy to involved areas. The schedules vary in different clinics, but in general the tendency is toward smaller doses given at more frequent intervals. Repetition is

frequently necessary. Gold has not been shown to offer relief. Early studies indicate cortisone to be effective in spondylitis.

The peripheral joints are managed as are those of the typical rheumatoid variety.

**PROGNOSIS.** When spinal ligaments have calcified and the apophyseal and sacroiliac joints fused, activity of the disease usually ceases. The severe pain abates, and unless the appropriate corrective measures have been undertaken, severe deformities will be present. Over 20 years may be required for activity to "burn out"; the average is in the neighborhood of 10 years.

### DEGENERATIVE JOINT DISEASE

**Definition.** In nearly all individuals past middle age, degenerative joint disease (hypertrophic arthritis, osteoarthritis, senile arthritis) is present to some extent. It is characterized by degeneration of cartilage, eburnation and overgrowth of contiguous bony surfaces, and little, if any, synovial reaction. In contradistinction to rheumatoid arthritis, this is a primary joint disease with no systemic manifestations. The pathologic changes may be primary or they may be secondary to trauma, to alterations in joint architecture subsequent to various destructive arthritides, to recurrent dislocations, to static trauma (knock-knees), and to other causes of faulty joint alignment. By no means do all individuals with the characteristic pathologic alterations of the disease have symptoms therefrom.

**Etiology.** In the natural process of aging, changes begin to appear in hyaline cartilage in the second and third decade. These consist of loss of elasticity, splitting of the matrix, development of small blisters on the surface, and linear grooves and pits in areas subjected to weight bearing. The cause of the aging process is obscure, but it is to be remembered that cartilage is an avascular tissue and depends upon synovial fluid for its nutrition. Furthermore, cartilage repairs itself poorly following trauma. The exposure of the joint to a wide variety of influences added to the naturally occurring degenerative process is thought to be the important factor in bringing about the changes of degenerative joint disease. Among these influences are faulty body mechanics such as poor posture, throwing strain on the spine, and genu valgum, putting stress on the knees. The alterations of joint architecture such as may occur after rheumatoid arthritis or the

infectious arthritides may hasten appearance of the disease. Trauma, as a consequence of weight bearing and motion, predisposes to the appearance of lesions. In the knee, for example, degenerative changes occur most frequently at the median horizontal facet of the patella and along the patellar groove of the femur, contiguous areas subject to friction. In summary, degenerative joint disease results from a combination of factors. These include the aging process of hyaline cartilage, its poor powers of repair, and the added burden of trauma to cartilage.

**Pathology.** The changes in cartilage consist of fraying, fibrillation, splitting of the matrix, and clustering of cells with advancing of the process. This is followed by the appearance of pitting, depressions, and, finally, erosions of the cartilage. The denuded bone assumes a different pattern, becomes eburnated with occasional cystlike areas. Cartilage opposite those changes may show minimal hypertrophic changes. At the margin of the joint, cartilage proliferates and, when converted into bone, results in formation of osteophytes. In contradistinction to the process in rheumatoid arthritis, the synovial membrane takes little or no part in the process; proliferation and pannus formation are absent, and ankylosis does not occur except under special circumstances. The villi may show some hypertrophy, become pedunculated, and finally break off to lie free in the joint cavity as "joint mice." It is convenient to look upon degenerative joint disease as a localized disease of joints. The aging of articular cartilage may, however, represent a more subtle, generalized process. Unlike rheumatoid arthritis, therefore, visceral lesions do not appear.

Many persons with the above mentioned changes are entirely free of symptoms. When pain does occur, it is most often associated with joint motion. It is thought that the rubbing together of the roughened, eburnated bony surfaces under such circumstances without the buffering effect of cartilage is responsible for the sensations evoked. Muscle pain and spasm from poor use of some muscles, with strain on others, secondary inflammation of fibrous tissues and bursae, and periosteal elevation may all contribute to discomfort.

**Epidemiologic and Environmental Factors.** Degenerative joint disease is world-wide in distribution. Furthermore, man is not the sole

victim of the process, as many animal species develop these changes. Skeletal remains of prehistoric man and animal have shown evidence of degenerative joint disease.

In a series of knees examined post mortem, there was no sex difference in the incidence of pathologic changes. There does appear to be a hereditary predisposition to the development of the degenerative change in cartilage. Moreover, obesity which shows definite familial trends is one of the frequent associated features.

Occupation plays some role in the progression of changes in so far as trauma to a joint may be a factor. Degenerative joint disease is apt to be pronounced in the shoulders of porters who carry heavy bags, in the knees of those whose occupation entails long hours of standing, and in the spine of those whose work entails strain to the back. The lumbar spine is involved more often in men than in women.

**Clinical Features.** Degenerative joint disease is responsible for symptoms in only about 5 per cent of all who are affected by the process. The disease is progressive but only rarely causes the invalidism that rheumatoid arthritis does. The joints most commonly affected are the knees, lumbar vertebrae, hips, cervical vertebrae, and terminal interphalangeal joints (Heberden's nodes, see p. 491). Rarely, the proximal interphalangeals and other joints may be involved.

Symptoms referable to degenerative joint disease begin insidiously. Stiffness and pain may be experienced on arising in the morning or on resuming motion after rest. With further activity to a certain point, relief is experienced. Continued activity and weight bearing bring a return of symptoms. This is to be contrasted to rheumatoid arthritis, in which pain may also occur at rest and become aggravated by motion. The localization of the process dictates the type of symptoms. In the lumbar spine the disease evokes sensations of stiffness and pain in low lumbar regions. Involvement of the cervical spine on occasion is responsible for stiffness of the neck and, rarely, for root pains radiating to the chest and down the arm. This is sometimes confused with angina pectoris. It cannot be stressed too emphatically that some "hypertrophic" changes will be seen in the spines of all persons and in many of younger age groups where trauma has been a factor. In only a few of these is the process responsible for symptoms.

Examination of a joint at any stage of the disease may reveal nothing of note. The heat, redness, and swelling of an acute arthritis is absent. Some enlargement and thickening may result from bony overgrowth. A grating sensation on motion, experienced by both patient and examiner, may be caused by "joint mice" and by rubbing together of roughened articular surfaces. Effusions are rare and, if present, usually connote the existence of an element of rheumatoid arthritis, the so-called "mixed arthritis." With involvement of the cervical spine, crepitation on motion of the neck may be noted, and symptoms of radiculitis may be reproduced by twisting the neck. Lumbar spine involvement can be demonstrated by the reproduction of pain when putting the spine through its range of motion. Radiation of pain along distribution of the sciatic nerve may occur.

**Diagnosis.** The roentgenographic findings in degenerative joint disease consist, in the early stages, of narrowing of joint spaces, formation of osteophytes at lateral articular margins, and slight disuse atrophy at ends of bones. As the cartilage undergoes further degeneration, the joint spaces are further narrowed and become irregular. Apposed bony surfaces become dense and eburnated, and marginal lipping becomes apparent. In contradistinction to rheumatoid arthritis, ankylosis is rare.

There are no characteristic laboratory findings in degenerative joint disease. It does not cause elevation of the sedimentation rate, anemia, or leukocytosis.

In many instances it is difficult to assess the role of the roentgenographic evidence of degenerative joint disease in the causation of symptoms, for it is realized that many persons have these findings and yet are free of symptoms. If, in a patient suspected of having degenerative joint disease, relief is not obtained by rest or by other physical measures, then one should suspect other causes for the pain. Other arthritides may coexist. Metastatic carcinoma should not be overlooked.

**Treatment.** The patient with degenerative joint disease can derive much benefit from an explanation of his disease. Such explanation should carry with it reassurances that crippling deformities will not ensue and that life expectancy will not be shortened. Too frequently patients are told, "Nothing can be done for you,"

and are left to drift to patent remedies and quack measures. They should be told that nothing can change the existing degenerative changes and that measures will be undertaken with the hope of relieving some of the trauma to joints, and to alleviate the pain. The treatment of each patient must be individualized.

The *relief of trauma* to a joint may consist of any number of measures. Obese patients with involvement of knees, hip, or spine should lose weight. This must be a rigid feature of the regimen, and strictly followed. Correction of postural defects will often relieve some of the trauma to weight-bearing joints. In those individuals in whom occupations seem to play a role in aggravating symptoms, attempts should be made to alter precipitating motions and stances. A pendulous abdomen may incite pain in a spine that is involved with the degenerative process. Weight loss and abdominal supports may afford marked relief. Symptoms produced by disease of the cervical spine can, to a large measure, be alleviated by the judicious use of a Thomas collar or gentle head traction. An elastic bandage or a leather-laced cuff will relieve some of the pain in the knees.

Physical measures play a major role in the therapy of this disease. Simple procedures that can be carried out at home are the best. Heat to joints offers marked relief in many cases. This can be applied in the form of hot towels, paraffin baths, an electric pad, or hot tubs. All methods of applying heat seem equally effective. Heat applied for periods of 10 to 20 minutes three times a day usually suffices.

Gentle massage of joints and periarticular structures sometimes affords relief. Massage should not be vigorous to the point of inciting pain. Limited exercises are valuable. Usually the patient will be able to increase his range of motion following application of heat. With involvement of knees, atrophy of the quadriceps may ensue. Exercises designed to strengthen this group of muscles are indicated. Rest should be employed, but not to the point of making the patient an invalid. One or two hours a day off the feet will diminish pain to a great extent. This, of course, need not apply to those whose affected joints are not part of the weight-bearing skeleton.

*Analgesics* play a definite role in the management of degenerative joint disease. Aspirin in

doses of 0.6 Gm. three to four times a day may afford considerable relief.

Many *miscellaneous measures* have been tried, but most without any striking improvement. Local procaine infiltration has not met with the success that it has in some cases of rheumatoid arthritis. No "internal medications," with the exception of salicylates, are of value. Various liniments applied to the joints do, at times, evoke a sense of well-being. The local heat that they produce and the gentle massage used in applying them cause the relief they sometimes bring.

**Prognosis.** With rare exceptions, degenerative joint disease does not result in crippling deformities. Most of the pathologic changes are irreversible. However, with the judicious use of measures outlined above, much of the pain and disability can be obviated to a large degree. The ultimate outcome in a given case depends to a large measure on the vigor and enthusiasm of the physician's approach, on his ability to analyze carefully and to remedy, where possible, all precipitating factors.

**Variants of Degenerative Joint Disease:**  
**HEBERDEN'S NODES.** These are knoblike deformities involving the distal interphalangeal joints and represent a part of the picture of degenerative joint disease. This mild form of the disease portrays the typical pathologic picture. The nodes occur in about 32 per cent of women past middle age and in about 3 per cent of men. There appears to be a definite familial trait. An intact nerve supply to the extremity is necessary for the development of the nodes. In one series of 94 women with Heberden's nodes, 12 had degenerative joint disease of other extremities, 34 had crepitus in the knees, and 19 complained of transient aches. In the control group of 109 women, degenerative joint disease occurred in 3 and crepitus of knees in only 25.

The nodes usually appear in middle age but may be noted in earlier life. The middle and index fingers are most often involved. Frequently, small cystic areas are noted at the lateral margin of the involved joints. Aspiration of these yields a gelatinous material. Heberden's nodes are frequently asymptomatic. At times they may become reddened and acutely painful.

Heberden's nodes are to be differentiated from rheumatoid arthritis. The latter most frequently involves the proximal interphalangeal joints, producing the fusiform swellings, and is accom-

panied by the systemic symptoms of the disease. In 10 per cent of cases, however, Heberden's nodes may occur in the proximal interphalangeal joints. Local heat in the form of hot towels or paraffin soaks are quite efficient therapeutic aids.

**COSTON'S SYNDROME.** This term refers to the somewhat rare entity of degenerative joint disease of the temporomandibular joint. It may be primary or secondary to "burned-out" rheumatoid arthritis. Tinnitus, deafness, headache, pain in the ear, and, rarely, herpes of the external auditory canal may be symptoms noted. Properly fitting dentures to obviate malocclusion frequently bring striking relief.

**MIXED ARTHRITIS.** In all patients with rheumatoid arthritis, pathologic changes of degenerative joint disease will eventually occur. The problem may then be that of management of the latter. The term "mixed arthritis" is most commonly used for those individuals past middle age in whom degenerative joint disease is a primary problem and in whom rheumatoid arthritis begins late in life and adds its ravages to the pre-existing joint disease. In a patient with degenerative joint disease, persistent pain at rest, periarticular swellings, and elevated sedimentation rate should strongly suggest the added rheumatoid element.

## POLYARTHRITIS AND FEVER

A febrile illness with accompanying polyarthritis is a frequent clinical entity, and one that may offer considerable difficulty in diagnosis. Many cases present an obvious diagnosis on first examination; other cases, however, defy all diagnostic attempts for long periods of time. The joint complaints vary from fleeting arthralgias to acutely swollen joints. Careful history and physical examination, use of appropriate laboratory procedures, and careful observation of patients will lead eventually to a correct diagnosis in most cases. Discussion of all diseases and syndromes concerned will be found in various chapters of this text. Table 45 contains a list of entities to be considered when confronted with such a problem. It is apparent that fever and polyarthritis, or polyarthritis alone, are unusual in many of these entities, but they may occur.

## TRAUMA AND JOINT DISEASE

Trauma, such as a fracture, dislocation or sprain, plays an obvious role in the causation and

Table 45

## CONDITIONS IN WHICH POLYARTHRITIS AND FEVER MAY BE NOTED, DIVIDED AS TO PROBABLE ETIOLOGIES

I. Infections	
A. Bacterial	
Gonococcic	
Meningococcic	
Brucellosis	
Syphilis (secondary)	
Haverhill fever	
Salmonella	
Bacterial endocarditis	
Bacillary dysentery	
"Septicemia"	
Rat bite fever ( <i>Spilillum minus</i> )	
B. Viral	
Lymphogranuloma venereum	
Rubella	
Mumps	
Infectious mononucleosis	
C. Parasitic	
Trichinosis	
D. Fungous	
Coccidioidomycosis	
II. Neoplastic	
Hodgkin's disease	
Carcinoma of lung	
III. Blood Dyscrasias	
Hemophilia	
Leukemia	
Sickle-cell anemia	
Henoch's purpura	
IV. Collagen Diseases	
Rheumatic fever	
Rheumatoid arthritis	
Lupus erythematosus	
Dermatomyositis	
V. Allergic	
Serum sickness	
Drug fever	
Periarteritis nodosa	
Erythema nodosum	
VI. Metabolic	
Gout	
Uremia	
VII. Unknown Etiology	
Reiter's syndrome	
Ulcerative colitis	
Erythema multiforme	
Porphyria	
Sarcoidosis	

perpetuation of joint disease. On the other hand, more subtle, minor, and repeated traumas may play a major role in the development of arthritis.

The current concept of degenerative joint disease, as outlined previously, would indicate that the repeated minor traumas of weight bearing and locomotion are of etiologic significance. In the case of rheumatoid arthritis, trauma to a joint will apparently, at times, favor localization of the disease process in the injured joint. Similarly, it is believed that trauma, as by a blow on the foot or the wearing of a tight shoe, may occasionally precipitate an attack of gout in the traumatized extremity. The development of neuropathic joint disease is facilitated by the repeated injury to a joint that is insensitive to pain.

As has been mentioned, many of the chronic arthritides, with ensuing trauma of disturbed joint function, often proceed into degenerative joint disease.

### PSYCHOGENIC RHEUMATISM

Emotional factors influence the course of all cases of chronic joint disease to some degree. Occasionally they seem to play a major role in precipitating relapses and in enhancing the severity of the disease. In some patients with mild or quiescent organic joint disease, psychogenic factors appear to be predominant in producing disability.

A different type of problem is posed by the patients in whom there are no objective clinical or laboratory findings, yet who present symptoms referable to the musculoskeletal system and in whom personality difficulties and emotional conflicts are obvious. To this group the term "psychogenic rheumatism" has been applied.

Psychogenic rheumatism assumed large proportions in the military experience of World War II, and in one hospital series comprised one sixth of the total patients admitted with articular complaints.

A previous history of psychoneurotic complaints can often be elicited. It is not unusual to find that friends or other members of the family are affected by a true arthritis.

In cases of pure psychogenic rheumatism, complaints are most frequently localized to the lower extremities and back. Camptocormia, or hysterical kyphosis, is common. The symptoms are often vague and may be described as "burning," "tightness," or "tension." They are apt to be made worse during emotional stress and are almost always aggravated by exercise. Methods which often afford relief to the arthritic joint, such as salicylates and the use of heat, are usually without benefit. The backache of psychogenic origin is usually not relieved by bed rest. The differentiation between psychogenic rheumatism, fibrositis, and early rheumatoid arthritis

may be quite difficult. However, careful correlation of complaints with the emotional background, a normal sedimentation rate, and the absence of objective joint findings are of considerable aid in diagnosis.

The treatment of psychogenic rheumatism may be quite difficult, particularly if on previous occasions the patient has been told by physicians that he has "arthritis." The confidence of the patient in his physician and in his reassurance that crippling deformities will not ensue, and the removal of unpleasant life situations, will often result in striking amelioration of symptoms. In some patients skillful psychotherapy may be needed.

### PALINDROMIC RHEUMATISM

The term "palindromic rheumatism" has been given to a rare syndrome manifested by transient articular or periarticular swellings recurring frequently over many years. The etiology is unknown. Because of the recurrent and transient nature of the syndrome it has been suggested that allergy might play a role, but there is no evidence to support this. Confusion exists as to the relationship between this syndrome and rheumatoid arthritis. Some believe it to represent a distinct entity, whereas others regard it as only one of the many clinical variants of rheumatoid arthritis. The latter concept is probably more nearly correct.

A limited number of synovial biopsies taken during acute attacks have demonstrated polymorphonuclear leukocytic infiltration within the synovial and subsynovial tissues. The lymphocytic nodules of rheumatoid arthritis are not found, cartilage is not destroyed, and pannus formation does not occur.

The syndrome occurs in the age group of rheumatoid arthritis. Each attack begins suddenly, usually toward evening, and may last only three hours, but usually one or two days and rarely as long as a week. Pain, swelling, and redness involve usually a single joint, though more than one may be affected. Periarticular swellings may occur either adjacent to or remote from involved joints. Painful red finger pads may be noted. Although practically any joint in the body may be involved, the proximal interphalangeals, metacarpophalangeals, knees, feet, and backs of the hands are the most frequent sites. The interval between episodes of palindromic rheumatism

may vary from a few hours to a year. The average number of attacks in a year was 23 in one series, although there were as many as 300 in one year in some patients. Episodes may recur for as long as two to three decades.

The noteworthy features of the syndrome are its ephemeral nature, the absence of constitutional symptoms, the absence of roentgenographic evidences of joint destruction, and the absence of deformities. The sedimentation rate is usually normal during an attack but may be slightly elevated.

Palindromic rheumatism is to be differentiated from rheumatoid arthritis, fibrositis, and psychogenic rheumatism. Before making a positive diagnosis of palindromic rheumatism one should see the actual swelling and redness during an acute attack and should be certain of the absence of permanent joint damage. Prolonged observation is necessary in order to be reasonably certain that the patient's disease will not eventually develop into classic rheumatoid arthritis.

The treatment of palindromic rheumatism is symptomatic.

### REITER'S SYNDROME

The eponym "Reiter's syndrome" designates a symptom complex comprising the triad of urethritis, arthritis, and conjunctivitis. At times diarrhea occurs, and a variety of other visceral lesions may be noted.

**Etiology and Epidemiology.** The etiology is unknown, but the weight of evidence has incriminated, either directly or indirectly, members of the pleuropneumonia-like group of organisms and the dysentery bacilli. The earlier finding of a spirochete in the blood of a patient with the syndrome has not been corroborated. Pleuropneumonia-like organisms have been isolated from the urethra of a few patients with Reiter's syndrome, and in rare instances these bacteria have been recovered from the synovial fluid. Since these organisms are difficult to detect, it is possible that they may play an important etiologic role and may have been overlooked for technical reasons. On the other hand, clinical observations for a number of years have suggested that bacillary dysentery is responsible for the development of the syndrome. A recent outbreak of dysentery in Finland lends weight to this credence. During the years 1943-46, 341 cases of Reiter's syndrome were observed on the

Karelian Isthmus, where bacillary dysentery was endemic. It was only rarely observed in other parts of Finland. The majority of cases occurred in 1944 when the dysentery assumed epidemic proportions. Moreover, the incidence of the syndrome closely paralleled the incidence of dysentery from season to season. Whereas the incidence of Reiter's syndrome was 0.2 per cent in patients with dysentery, dysentery preceded the onset of the syndrome in 96.4 per cent of the cases. In the United States, however, it has been unusual to observe this relationship. Reiter's syndrome usually affects young adult males but can affect females and all age groups.

**Pathology.** A limited number of microscopic examinations of synovial tissue have demonstrated some villous formation, hyperemia, and infiltrates of lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. The cellular infiltrates do not assume the nodular pattern observed in rheumatoid arthritis, and pannus formation is not seen.

**Clinical Features.** Urethritis, conjunctivitis, and polyarthritis usually follow each other in that order with from two to forty days being required for the complete syndrome to manifest itself. The urethritis varies from a slight serous discharge to a profuse purulent one. Occasionally blood may be noted. It is, as a rule, more scanty than is that of gonorrhea. The urethritis is of short duration in most instances and ceases before the onset of arthritis. In those cases in which it persists for several months, the symptoms wax and wane in intensity. Conjunctivitis, usually bilateral, runs the gamut from a mild injection of the bulbar conjunctivas to an intense purulent conjunctivitis. Its duration is variable but is shorter than that of arthritis. Keratitis, iridocyclitis, and corneal ulceration may be noted. Arthritis is most often polyarticular and involves principally weight-bearing joints—in particular, ankles and knees. The small joints are only occasionally involved. Joint involvement is frequently of sudden onset, several joints being affected within two or three days. Heat, redness, and swelling, both articular and periarticular, are noted. Arthralgias without objective findings rarely occur. The articular involvement persists from one month to over a year in some instances. It always remains after the other features of the syndrome have subsided. Involvement of tendons, tendon sheaths, and bursae may be noted.

Among the *other manifestations* of Reiter's syndrome are the cutaneous lesions of keratoderma blennorrhagica, ulcerations of the penis, ulcerative lesions of the oral cavity, cystitis, proteinuria, pleuritis, pericarditis, and myocarditis. Diarrhea, which may be quite mild, has been reported to precede most cases of Reiter's syndrome by several weeks. The occurrence of diarrhea, as mentioned above, has been particularly striking in the various series reported from military hospitals and in the Finnish group.

The course of Reiter's syndrome is exceedingly variable. Some patients are afebrile during the entire course of the disease, while others may develop temperatures as high as 104° F. during the early stage of the disease. Recurrences which may occur from weeks to years after the initial episode are characteristic of the syndrome. The recurrence may assume the pattern of the original attack or may consist of any combination of the triad. It is probable that permanent destructive joint changes do not take place.

**Diagnosis.** The diagnosis of Reiter's syndrome by definition should be limited to those cases presenting the classic triad. There has been a tendency to accept some cases in which certain features of the syndrome were lacking. The chief diagnostic problem lies in its differentiation from gonococcal arthritis in which urethritis, conjunctivitis, and arthritis may occur. Careful cultural studies and the use of the gonococcal complement-fixation test will usually clear up the dilemma. Attempts should be made to isolate members of the pleuropneumonia group of organisms from the urethra and from the joint fluid.

**Treatment.** Salicylates may be of value for the relief of pain. The physical measures of rest, heat, massage, muscle-setting exercises, and splints such as described for patients with rheumatoid arthritis should be undertaken. Recent evidence indicates that streptomycin in doses of 2.5 Gm. daily for 10 days may shorten the course of the disease. This further suggests the etiologic significance of pleuropneumonia-like organisms, since these bacteria are susceptible to this antibiotic.

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Part IV  
METABOLIC AND ENDOCRINE DISORDERS

EDITOR: GEORGE W. THORN

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# 40

## General Considerations

William J. Darby

Excess Zone
Saturated Zone
Unsaturated But Functionally Unimpaired Zone
Potential Deficiency Disease
Latent Deficiency Disease
Clinically Manifest Deficiency Disease

The body has a dietary requirement for calories, protein, vitamins, minerals, and perhaps fat. It is obvious that inorganic nutrients cannot be synthesized in the body and must be derived from exogenous sources. Of the organic nutrients, some can be synthesized by the body from various precursors (carbohydrates, fats, or protein); thus the nonessential amino acids may be built up within the organism so that they do not have to be supplied in the diet. On the other hand, some organic materials cannot be made by the organism, and, since they play an essential metabolic role, it is necessary that they be supplied in the diet. This latter group includes the vitamins, the essential amino acids, and the essential fatty acids. In some species it has been demonstrated that the organism may have a limited capacity to make a given metabolite and that this capacity may be exceeded only under certain conditions of stress in which there appears a dietary requirement for the nutrient.

One should note that vitamins are merely a part of the group of metabolites which the body cannot synthesize and, accordingly, they are, as a group, endowed with no more mysterious or magical power than any other essential nutrient.

The spectrum of nutriture ("condition as to nourishment") ranges from the zone of excess to that of the severe clinically manifest deficiency disease. The following zones have been defined:

**1. Excess Zone.** The state in which body harm results from the high level of the nutrient in the body. Examples of excess are obesity and hypervitaminosis A or D.

**2. Saturated Zone.** The state in which the body is incapable of increasing its content of a

given nutrient and, accordingly, fails to retain additional quantities of the administered nutrient. This zone is usually considered in relation to the water-soluble vitamins (ascorbic acid, B vitamins).

**3. Unsaturated But Functionally Unimpaired Zone.** That level at which the body contains less of the nutrient than at saturation, but at which no clinically manifest or potential deficiency disease exists, and no known biochemical or physiologic tests indicate functional impairment.

**4. Potential Deficiency Disease.** A zone which exists with absence of clinical signs of a deficiency but in which (a) a new stress on the organism will cause rapid development of the clinically manifest disease or (b) suitable biochemical or physiologic tests yield evidence of decreased reserve functional capacity. Reserve functional capacity is defined as the ability of the organism to withstand a stress without deviation from its usual physiologic course.

**5. Latent Deficiency Disease.** This is the mildest clinically detectable deficiency state. It is characterized by vague, indefinite, nonspecific symptoms which are suggestive, but which do not permit a definite diagnosis. The diagnosis is established on the history, by therapeutic trial, and with the aid of biochemical tests.

**6. Clinically Manifest Deficiency Disease.** This zone includes both mild and severe states. The above classification eliminates the use of the ambiguous term "subclinical deficiency disease."

A lower nutriture, and thereby a deficiency disease, may result from a decreased dietary intake of a nutrient or from a conditioning factor (disease) which increases the demand for the nutritive essential. Such conditioning factors include states with impaired absorption (e.g., sprue syndrome, pernicious anemia, or residual effects of such operative procedures on the gas-

Table 46

RECOMMENDED DAILY DIETARY ALLOWANCES<sup>1</sup>  
Revised 1948

Food and Nutrition Board, National Research Council

	Calories <sup>2</sup>	Protein Gm.	Ca Gm.	Fe Mg.	A <sup>3</sup> I.U.	B <sub>1</sub> <sup>4</sup> Mg.	Ribo. <sup>4</sup> Mg.	Niacin <sup>4</sup> Mg.	C Mg.	D I.U.
Man (154 lb., 70 kg.)										
Sedentary.....	2400	70	1.0	12 <sup>5</sup>	5000	1.2	1.8	12	75	6
Physically active.....	3000	70	1.0	12 <sup>5</sup>	5000	1.5	1.8	15	75	6
With heavy work.....	4500	70	1.0	12 <sup>5</sup>	5000	1.8	1.8	18	75	6
Woman (123 lb., 56 kg.)										
Sedentary.....	2000	60	1.0	12	5000	1.0	1.5	10	70	6
Moderately active.....	2400	60	1.0	12	5000	1.2	1.5	12	70	6
Very active.....	3000	60	1.0	12	5000	1.5	1.5	15	70	6
Pregnancy (latter half).....	2400 <sup>7</sup>	85	1.5	15	6000	1.5	2.5	15	100	400
Laetation.....	3000	100	2.0	15	8000	1.5	3.0	15	150	400
Children up to 12 yrs. <sup>8</sup>										
Under 1 yr. <sup>9</sup> .....	110/2.2 lb (1 kg.)	3.5/2.2 lb. (1 kg.)	1.0	6	1500	0.4	0.6	4	30	400
1-3 yrs. (27 lb., 12 kg.).....	1200	40	1.0	7	2000	0.6	0.9	6	35	400
4-6 yrs. (42 lb., 19 kg.).....	1600	50	1.0	8	2500	0.8	1.2	8	50	400
7-9 yrs. (58 lb., 26 kg.).....	2000	60	1.0	10	3500	1.0	1.5	10	60	400
10-12 yrs. (78 lb., 35 kg.).....	2500	70	1.2	12	4500	1.2	1.8	12	75	400
Children over 12 yrs. <sup>8</sup>										
Girls, 13-15 yrs. (108 lb., 49 kg.)...	2600	80	1.3	15	5000	1.3	2.0	13	80	400
16-20 yrs. (122 lb., 55 kg.)...	2400	75	1.0	15	5000	1.2	1.8	12	80	400
Boys, 13-15 yrs. (108 lb., 49 kg.)...	3200	85	1.4	15	5000	1.5	2.0	15	90	400
16-20 yrs. (141 lb., 64 kg.)...	3800	100	1.4	15	6000	1.7	2.5	17	100	400

<sup>1</sup> Objectives toward which to aim in planning practical diets: The recommended allowances can be attained with a good variety of common foods which will also provide other minerals and vitamins for which requirements are less well known.

<sup>2</sup> Calorie allowances must be adjusted up or down to meet specific needs. The calorie values in the table are therefore not applicable to all individuals but rather represent group averages. The proper calorie allowance is that which over an extended period, will maintain body weight or rate of growth at the level most conducive to well-being.

<sup>3</sup> The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.

<sup>4</sup> For adults (except pregnant and lactating women) receiving diets supplying 2000 calories or less, such as reducing diets, the allowances of thiamine and niacin may be 1 mg. and 10 mg., respectively. The fact that figures are given for different calorie levels for thiamine and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation. In the present revision, riboflavin allowances are based on body weight rather than calorie levels. Other members of the B complex also are required, though no values can be given. Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remaining B vitamins.

<sup>5</sup> There is evidence that the male adult needs relatively little iron. The need usually will be provided for if the diet is satisfactory in other respects.

<sup>6</sup> The need for supplemental vitamin D by vigorous adults leading a normal life seems to be a minimum. For persons working at night and for nuns and others whose habits shield them from the sunlight, as well as for elderly persons, the ingestion of small amounts of vitamin D is desirable.

<sup>7</sup> During the latter part of pregnancy the calorie allowance should increase to approximately 20 per cent above the preceding level. The value of 2400 calories represents the allowance for pregnant, sedentary women.

<sup>8</sup> Allowances for children are based on the needs for the middle year in each group and are for moderate activity and for average weight at the middle year of the age group.

<sup>9</sup> Needs for infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk.

(Continued on facing page.)

trointestinal tract as gastrectomy or short-circuiting operations), excessive loss (e.g., iron loss in chronic bleeding), or increased requirement (e.g., hyperthyroidism, growth, pregnancy, or lactation).

Dietary deficiencies may occur under conditions which restrict the variety of foods consumed. The displacement of food by alcohol may eventually result in the development of deficiency manifestations because of the decreased intake of protein, thiamine, niacin, etc. Due to metabolic relationships the requirement of some nutrients may be higher on one diet than on another. Thus, thiamine requirement is higher on the high-carbohydrate-low-fat dietary of the Orient than on the usual Western diet.

The most common form of malnutrition is caloric excess or obesity. Florid deficiency states of dietary origin are encountered infrequently in the United States at the present, but they were

more prevalent in the past. Clinically manifest deficiency states in the adult are usually of the "conditioned" type, although in some areas it is not unusual to encounter cases of deficiencies arising from the displacement of food with alcohol.

Although food-faddists, alcoholics, and persons on greatly restricted therapeutic diets may develop deficiency diseases regardless of their economic position, among the middle and upper economic groups the most frequently encountered deficiency diseases are conditioned ones. Dietary deficiencies are met more often among the economically underprivileged groups, and hence are more prevalent in wards of charity hospitals than in private institutions.

In any consideration of vitamin deficiency states it is useful to make certain generalizations: The absorption, storage, and excretion of vitamins seem to follow two broad patterns. Water-

(Table 46—Continued)

#### FURTHER RECOMMENDATIONS:

**Fat.** There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiologic requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals, the human needs for these fatty acids are not known. In spite of the paucity of information on this subject, there are several factors which make it desirable (1) that fat be included in the diet to the extent of at least 20 to 25 per cent of the total calories and (2) that the fat intake include essential unsaturated fatty acids to the extent of at least 1 per cent of the total calories. At higher levels of energy expenditure, e.g., for a very active person consuming 4500 calories and for children and for adolescent persons, it is desirable that 30 to 35 per cent of the total calories be derived from fat. Since foodstuffs such as meat, milk, cheese, nuts, etc., contribute fat to the diet, it is necessary to use separated or "visible" fats such as butter, oleomargarine, lard, or shortenings to supply only one-third to one-half the amounts indicated.

**Water.** A suitable allowance of water for adults is 2.5 liters daily in most instances. An ordinary standard for diverse persons is 1 ml. for each calorie of food. Most of this quantity is contained in prepared foods. At work or in hot weather, requirements may reach 5 to 13 liters daily. Water should be allowed *ad libitum*, since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons.

**Salt.** The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 Gm. daily, except for some persons who sweat profusely. The average normal intake of salt is 10 to 15 Gm. daily, an amount which meets the salt requirements for a water intake up to 4 liters daily. When sweating is excessive, an additional gram of salt should be consumed for each liter of water in excess of 4 liters daily. With heavy work or in hot climates, 20 to 30 Gm. daily may be consumed with meals and in drinking water. Even then, most persons do not need more salt than usually occurs in prepared foods. It has been shown that, after acclimatization, persons produce sweat that contains only about 0.5 Gm. to the liter, in contrast with a content of 2 to 3 Gm. for sweat of the unacclimatized person. Consequently, after acclimatization, need for increase of salt beyond that of ordinary food disappears.

**Iodine.** The requirement for iodine is small, probably about 0.002 to 0.004 mg. daily for each kilogram of body weight, or a total of 0.15 to 0.30 mg. daily for the adult. This need is met by the regular use of iodized salt; its use is especially important in *adolescence* and *pregnancy*.

**Phosphorus.** Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults, the phosphorus allowances should be approximately 1.5 times those for calcium. In general, it is safe to assume that, if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus.

**Copper.** The requirement for copper for adults is about 1 to 2 mg. daily. Infants and children require approximately 0.05 mg. for each kilogram of body weight. The requirement for copper is approximately one-tenth that for iron. A good diet normally will supply sufficient copper.

**Vitamin K.** The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and for the first few days after birth. Supplemental vitamin K is recommended during the last month of pregnancy. When it has not been given in this manner, it is recommended for the mother preceding delivery or for the baby immediately after birth.

**Folic Acid.** The quantitative requirement cannot be estimated closely from evidence now available.

soluble vitamins (ascorbic acid, B-complex group) are diffusible, and examples of impaired absorption (except for vitamin B<sub>12</sub> in pernicious anemia) are not common; these factors may be stored in amounts sufficient to prevent the development of clinically manifest deficiency states over a period of deprivation of four months to a year or so; they (or their metabolic products) are excreted in the urine, and, hence, the accumulation of toxic quantities from excessive doses is not easy. The fat-soluble factors (carotene, vitamins A, D, E, and K) are absorbed along with lipids, and derangements of their absorption are seen in steatorrhreas and biliary obstruction; the body has great storage capacity for these factors, and it often requires upward of a year of deprivation of the adult to obtain evidence of clinically manifest deficiency; they are not excreted in the urine of healthy subjects, and may accumulate to toxic levels if grossly excessive quantities are given repeatedly. Representatives of both classes may be synthesized by the intestinal flora of man.

The signs of mild clinically manifest deficiency disease are nonspecific and are often simulated by non-nutritional causes. Only those signs due to deficiency will respond to nutritional therapy, and their response is usually quite rapid. Failure to understand these principles has resulted in much useless supplementation of patients with a great variety of preparations containing vitamins. False reliance on vitamin therapy has sometimes resulted in delayed institution of effective treatment.

To date the therapeutic effectiveness in man of the following vitamins has been clearly demonstrated: vitamin A and carotene, vitamin D, vitamin K, ascorbic acid, thiamine, riboflavin, niacin, folic acid (pteroylglutamates), and vitamin B<sub>12</sub>.

There is no convincing demonstration of clinically recognizable syndromes which are due to a deficiency of pyridoxine, pantothenic acid, biotin, tocopherols, or other vitamins required by lower species. Claims for the efficacy of pyridoxine in the nausea of pregnancy, irradiation sickness, acne, fissures of the angles of the mouth, etc., all await critical appraisal. Panto-

thenic acid and biotin hold a similarly uncertain position in human nutrition. Despite the numerous claims of spectacular therapeutic results from administration of large doses of tocopherols in a variety of obscure clinical conditions, there seems to exist no critically designed study which would substantiate these claims. These limitations of knowledge do not allow us to deny that these several factors may serve essential metabolic roles in man; they do permit the conclusion that to date there has been no demonstration of their usefulness in treating deficiencies. It may be that these substances are required in exceedingly small quantities and sufficient quantities are ingested in even very restricted diets; that they are synthesized and absorbed within the gastrointestinal tract; or that they can be synthesized by the human body.

Exact quantitative statements of daily minimal requirements of nutrients cannot be made. A useful "objective toward which to aim in the planning of practical dietaries" is provided by the Recommended Daily Dietary Allowances compiled by the Food and Nutrition Board of the National Research Council (table 46). These allowances are purposely sufficiently generous to maintain normal individuals in the zones of saturation or unsaturation without functional impairment. The allowances can be met by ingestion of a variety of readily available foods *without supplementation*. Revision (usually downward) of these standards has been made as more exact knowledge has developed, and future revisions may similarly be expected. As a general guide, the approximate range of satisfactory therapeutic dosage of the vitamins is 5 to 10 times the recommended daily allowance.

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## Undernutrition

George W. Thorn

### Total Caloric and Protein Deficiency

Nitrogen Balance

### Amino Acid Deficiency

Vitamin Deficiency

### Mineral Deficiencies

Sodium and Chloride

Potassium

Phosphate

Calcium

Magnesium

Iodine

Iron

Trace Elements

### Summary

Undernutrition is a serious medical problem in the world at large. Severe undernutrition incapacitates individuals and whole nations and predisposes to disease. It reduces efficiency and interferes seriously with reproduction and growth.

Undernutrition comprehensively includes a deficiency of one or more of the multiple essential dietary constituents. Obviously the requirement of calories, of essential amino acids, of minerals, and of vitamins will vary widely among adults, depending upon their occupation, and among all ages and sexes, depending upon the varying requirements for growth, pregnancy, and lactation. Many disease states are associated with increased specific as well as total needs. Finally, the efficiency with which the gastrointestinal tract absorbs essential materials deserves special consideration.

Undernutrition will be considered under the following categories:

1. Total caloric and protein deficiency.
2. Amino acid deficiency.
3. Vitamin deficiency.
4. Mineral deficiencies.

### TOTAL CALORIC AND PROTEIN DEFICIENCY

It is not possible to maintain nitrogen balance with a caloric intake insufficient to maintain ideal weight. It is possible, however, to maintain body weight with an adequate caloric intake despite deficiencies in protein, minerals, or vitamins. Maintenance of weight is the simplest and most accurate indication of an adequate caloric

intake except under conditions of abnormal sodium, chloride, and water retention which occur physiologically during the premenstrual period and pathologically in the presence of cardiac, renal, vascular, and hepatic disease. Under such circumstances patients may lose essential body tissue but conceal the fact by simultaneously retaining sodium, chloride, and water. In patients with mild or severe anorexia nervosa, undernutrition and specific deficiencies may develop as a consequence of psychologic and emotional difficulties preventing the intake of an adequate diet. In addition, in rare instances, specific nutritional deficiencies develop because of "end organ" failure rather than deficient diet—for example, cretinism and congenital heart disease with cyanosis. Special attention must be given to the completeness with which ingested food is absorbed as well as to abnormal losses which may occur from draining sinuses and fistulas following surgery, from extensive burns and external tissue injury, and from excessive perspiration, vomiting, and sputum. In addition to these are the abnormal losses associated with galactorrhea, melena, menorrhagia, hemoptysis, and kidney disease.

With continued suboptimal intake of essential dietary constituents, depletion of body reserves will occur. In the initial stage of deficiency there are neither chemical nor clinical manifestations. As the deficiency progresses, chemical and occasionally pathologic disturbances become detectable. Later the classic clinical syndrome develops in association with biochemical and pathologic lesions (fig. 91).

Preclinical deficiencies may be detected by tolerance tests. For example, in the presence of protein deficiency an increase in methionine intake may convert a negative to a positive nitrogen balance; in the presence of vitamin A deficiency the administration of a large test dose of the vitamin may fail to induce the expected normal rise in blood level. As the deficiency progresses, it may be possible to detect hypopro-

teinemia in cases of protein deficiency or a lowering of serum vitamin A level. Definitive clinical manifestations may be absent at this time, although efficiency may be impaired. As the deficiency progresses, clinical and pathologic changes

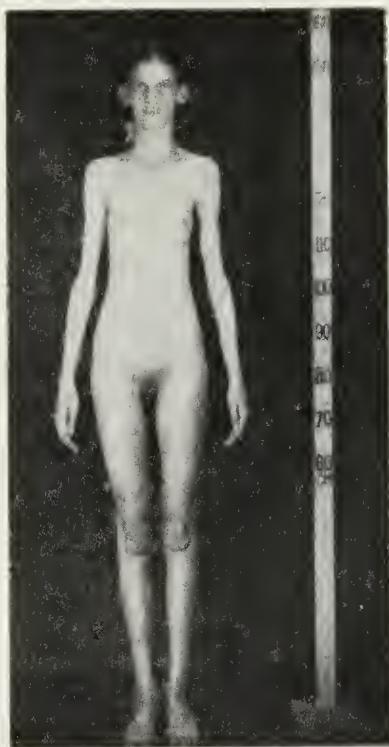


FIG. 91. A patient showing signs of marked undernutrition due to anorexia nervosa.

occur—i.e., hypoproteinemia leading to generalized edema, and vitamin A deficiency resulting in night blindness. Treatment of the deficiency by appropriate replacement therapy is followed by correction of the underlying changes in reverse order—i.e., improvement in the clinical syndrome, disappearance of the biochemical abnormalities, and finally restoration of the normal reserves of these constituents.

Since most instances of undernutrition are due to an inadequate total caloric intake, body fat and protein are called upon to supply additional calories for energy requirements. One gram of fat yields 9 calories, whereas 1 Gm. of carbohydrate or protein yields 4 calories. Because of the essentiality of protein to the preservation of homeostasis, the body conserves its tissue protein stores and mobilizes fat in so far as is possible. An obese individual is able to withstand starvation with considerably less serious consequences than one with limited fat reserves. Initial carbohydrate stores play an insignificant part in protection from starvation, as the available glycogen

supplies in the liver are exhausted within a day or two at the most by starvation, and must be replaced by glucose derived from body protein (gluconeogenesis). Most of the body tissue, with the exception of the brain, is capable of using fatty acids and ketone bodies as a ready source of energy. In starvation or undernutrition, maximum utilization of ketone bodies and fatty acids takes place with conservation of available glucose for those tissues which are unable to use fat as an immediate source of energy. By this shift in fat stores as the principal source of energy, the body is able to preserve its integrity by calling upon protein to a limited extent as a source of glucose. It is interesting, in this connection, to compare the ketonuria and ketonemia of starvation with that observed in unregulated diabetes mellitus. In the former the ketone and fatty acid production exceeds only slightly the tissue utilization. Hence, the ketone level of the blood is elevated only moderately. The renal threshold for ketone bodies may not be exceeded or, if so, only slightly; thus ketonuria may be absent or slight. In obese individuals the ketonuria may be greater during the early phase of starvation than in other individuals—the latter of necessity utilizing more body protein, hence forming more glucose. In unregulated diabetes mellitus the rate of production of ketone bodies and fatty acids bears no relation to body needs, and hence very high levels of blood ketones may occur and ketonuria may be severe. This uncontrolled ketone and fatty acid production appears to be an integral part of the diabetic syndrome. It is apparent from this that a patient with unregulated diabetes will suffer more rapid deterioration with inadequate caloric intake than will a normal individual.

A second important mechanism which the body employs for conservation of energy in the presence of undernutrition is a concomitant reduction in basal metabolic level. By this means the body reduces its energy requirements at the expense of initiative and drive. When undernourished individuals are forced to carry on heavy labor, deterioration is rapid and the chance for survival correspondingly poorer.

If access to water and minerals is limited in the presence of caloric deficit, a still greater stress is imposed upon the organism, as the effects of starvation are ameliorated by an adequate fluid and mineral intake. An adequate fluid intake

aids the kidneys in removing waste products of metabolism, maintains an effective circulation, and assists in the regulation of body temperature.

The effect of undernutrition is aggravated by extremes in temperature. Exposure to cold increases the caloric requirement, whereas exposure to heat above body temperature increases circulatory and ventilatory activity in an attempt to prevent hyperthermia. Hyperthermia increases the rate of catabolic processes within the body.

Specific deficiency syndromes rarely develop with undernutrition secondary to total caloric deficiency alone. This is in marked contrast to the frequency with which specific deficiency syndromes occur in individuals on an adequate total caloric intake, but deficient in one or more essentials.

### NITROGEN BALANCE

Whenever caloric intake becomes inadequate for energy requirements, a negative nitrogen balance develops. This is due to the fact that body protein is called upon to supply, in part, the calories required for energy. Thus, any individual with an inadequate caloric intake over any appreciable period suffers some degree of protein deficiency. In contrast, nitrogen balance may be maintained quite satisfactorily on a diet of relatively low protein content, provided an excess of fat and carbohydrate is available. This phenomenon is known as the "protein-sparing" action of carbohydrate and fat. Carbohydrate is more effective in this respect than fat because it is capable of supplying essential glucose which relieves the organism of the necessity of breaking down protein to form carbohydrate (gluconeogenesis). Fat is capable of sparing total calories, but not of supplying adequate glucose for body needs. Thus, an individual whose normal food intake consists of 300 Gm. of carbohydrate, 100 Gm. of fat, and 100 Gm. of protein may have his protein reduced to 40 to 50 Gm. daily and still maintain satisfactory nitrogen balance, provided he is able to increase his fat and carbohydrate intake sufficiently to supply the necessary total calories. At this point, however, a further consideration arises. Protein intake is capable of maintaining nitrogen balance only in so far as *all essential amino acids* are ingested and absorbed in adequate quantity. With a daily intake of 100 Gm. of protein, one is practically

assured of an adequate supply of the various essential amino acids. However, with a protein intake reduced to 50 Gm. or less, it is necessary for the diet to contain an adequate quantity of all essential amino acids (table 47) if nitrogen

Table 47  
AMINO ACIDS

<i>Essential</i>	<i>Nonessential</i>
Arginine	Alanine
Histidine	Aspartic acid
Isoleucine	Citrulline
Leucine	Cystine
Lysine	Glutamic acid
Methionine	Glycine
Phenylalanine	Hydroxyglutamic acid
Threonine	Hydroxyproline
Tryptophane	Norleucine
Valine	Proline
	Serine
	Tyrosine

balance is to be preserved, even though adequate calories in fat and carbohydrate are supplemented. The smaller the total daily protein intake, the higher the relative "biologic value" or completeness of that protein must be in order to maintain a satisfactory nutritional state. Thus, it is readily possible for individuals on a high-carbohydrate diet to develop protein deficiency because of inadequate protein intake or the ingestion of protein of low biologic value. In many instances in urban areas in the United States, deficiencies of this type are the result of "diet fads" or poorly supervised medical care. Thus, a physician may inadvertently suggest that a patient with slight proteinuria eat no eggs, meat, or milk. If such a diet is followed carefully for any period of time, it is apparent that the individual will ultimately suffer from two diseases—i.e., the initial kidney ailment now complicated by protein deficiency!

Protein deficiency may also become manifest not primarily because of reduced intake, but rather because of increased needs. Infants and children during periods of rapid growth will require much larger quantities of protein per kilogram of body weight than will adults. Pregnancy and lactation impose a tremendous increase in requirement of both calories and protein. This is also true of men carrying on hard physical labor. The protein requirement also is increased with febrile illnesses and following operations and infections.

Despite a normal protein intake, a negative

nitrogen balance may develop in certain gastrointestinal diseases such as pancreatic deficiency, regional enteritis, or ulcerative colitis, because of increased intestinal motility or deficient intestinal enzymes and secretions. Parenteral therapy, thus far, is rarely capable of maintaining nitrogen balance, despite the administration of relatively large quantities of whole blood, plasma, human albumin, or amino acid solutions because of the difficulty of providing an adequate *total caloric intake*. In the absence of a suitable preparation of fat for parenteral administration, it is almost impossible to provide an adequate total calorie intake. Hence, despite the administration of large quantities of protein or amino acid solutions, a negative nitrogen balance persists until the patient is able to ingest food.

In patients with prolonged or profuse bleeding from any source, one may encounter clinical evidence of protein deficiency. Under these circumstances, inadequacy in dietary protein intake will almost certainly precipitate a negative nitrogen balance and clinical symptoms of protein deficiency.

In conclusion, from the public health viewpoint, protein deficiency is prone to occur in areas of the world in which the principal items of diet contain a protein of relatively poor biologic value, associated with a deficiency in total caloric intake. From the individual physician's point of view, protein deficiency among private patients is most likely to occur under circumstances which prevent an adequate food intake (this is especially true of gastrointestinal diseases and allergies), a condition which in many instances is further complicated by excessive nitrogen loss from diarrhea, draining sinuses, hemorrhages, etc. In addition, "food faddists" constitute an important group of individuals who may develop protein deficiency despite a good economic level and a sound gastrointestinal tract.

#### AMINO ACID DEFICIENCY

Although specific amino acid deficiencies may complicate the picture of severe nutritional deficiency, the multiple deficiencies present under most circumstances make it impossible to distinguish syndromes due to particular amino acid deficiencies. With diseases such as hepatitis or cirrhosis, chronic nephritis, or thyrotoxicosis, abnormal metabolism of one or more of the essential amino acids may take place, or the require-

ment of one or more may be specifically increased. For example, in severe thyrotoxicosis large quantities of creatine escape from the muscles and are excreted in the urine. It is known that arginine and glycine unite in the kidney to form glyco-cyamine which, in turn, is methylated in the liver (methionine and choline) to form creatine. Thus, thyrotoxicosis necessitates an increased supply of at least three essential amino acids—i.e., arginine, glycine, and methionine, of which only glycine is synthesized within the body in quantities adequate for normal needs. In acute or chronic nephritis large quantities of albumin, a protein of very high biologic value, may be excreted and in certain inborn errors of metabolism, such as alkaptonuria or phenylpyruvic oligophrenia, essential amino acids or their intermediate degradation products may be excreted in the urine in large quantities.

Deficiency of sulfur-containing amino acids shows up readily with abnormalities in the growth of the skin, nails, and hair, all of which contain proteins with high sulfur-amino acid content. Methionine is also important, along with choline, as a source of "methyl groups" for many important liver functions. Deficiency of these is associated with fatty degeneration and infiltration of the liver. Other amino acids cause less striking individual manifestations, but usually induce negative nitrogen balance with loss of muscular strength, osteoporosis, hypoproteinemia with edema, and deterioration of the organism. The most striking constitutional symptoms are lassitude and weakness. It is difficult to differentiate between deficiency symptoms due to amino acid inadequacy and those resulting from hypovitaminosis or avitaminosis.

Essential amino acid deficit will not occur in individuals provided with 1 Gm. of protein per kg. of body weight, and adequate caloric intake, unless accompanied by some chronic organic disease. With reduction in protein intake below 0.5 Gm. per kg. per day, the biologic value of the protein must be excellent and the total caloric intake increased if deficiency is to be prevented. Low protein intake combined with low caloric intake will almost certainly lead to chronic amino acid deficiency.

#### VITAMIN DEFICIENCY

Specific vitamin deficiencies may color the clinical picture of more generalized nutritional

inadequacy. There are also numerous instances in which total caloric and protein intake is adequate, but in which a deficiency of one or more vitamins occurs. A good example of this is the difficulty which developed in attempting to provide an adequate supply of vitamin C during the long ocean voyages of the past century. The distribution of vitamin C among green vegetables and fresh fruits made this deficiency particularly prone to appear among sailors. Vitamin D deficiency is more likely to occur among children, particularly in cold climates with little sunshine, or in warm climates where custom encourages the complete covering of the body with clothing, thus depriving the child of the natural means of supplying himself with adequate D from solar radiation. Pellagra in the southern United States may occur in the presence of an adequate intake of total calories associated with an inadequate intake of niacin and the essential amino acid tryptophane. It seems probable that the vitamin requirement may vary considerably with the type of diet ingested.

Specific vitamin deficiencies are discussed in Chapters 43-48. It is well to point out here that there may be an increased need for certain vitamins in patients who are being fed for any prolonged period by a relatively *synthetic diet* (intravenous glucose); also, patients with disturbed carbohydrate metabolism such as accompanies diabetic acidosis may require large quantities of the B-complex vitamins when the rate of glucose utilization is suddenly and tremendously increased, as occurs with the institution of insulin therapy.

The most certain method of preventing vitamin deficiency is to ingest a well-rounded diet. Although foods from various parts of the country may differ widely in their mineral and vitamin content, if food is prepared properly and if a diversified diet is ingested, little opportunity exists for the development of vitamin deficiency except in the presence of particular or peculiar organic disease.

With the present custom of *massive* vitamin supplementation on the part of the American public, most individuals will exceed by several fold their daily needs. In some instances this may lead to carelessness in the selection of foods, with resultant amino acid or mineral deficiencies, although caloric and vitamin intake may continue to be optimal.

## MINERAL DEFICIENCIES

Mineral deficiencies may develop in accompaniment with serious undernutrition, or more specifically in the presence of renal disease or hormonal disturbances. With severe undernutrition there is loss of sodium, chloride, and water from the extracellular compartment of the body, as well as loss of potassium, magnesium, calcium, and phosphorus from tissue breakdown. Mineral deficiencies are most likely to develop during growth, pregnancy, lactation, and excessive menstruation; also in the presence of impaired renal function, gastrointestinal diseases associated with reduced intake or absorption and increased perspiration, copious sputum, or draining fistulas; and, finally, in the presence of adrenal cortical deficiency or excess, hyperparathyroidism, and diabetes mellitus.

### SODIUM AND CHLORIDE

The greater part of the sodium and chloride in the ordinary daily diet is obtained by adding sodium chloride as a seasoning. A deficiency of these electrolytes rarely occurs in normal individuals despite a low dietary intake, however, because of the efficient conservation of sodium and chloride by normal kidney function. In most instances sodium and chloride deficiency is caused by excessive loss of these electrolytes from the gastrointestinal tract associated with vomiting and diarrhea. Less frequently, deficiency of these electrolytes is observed in patients with pyelonephritis, adrenal cortical insufficiency, and diabetes mellitus. Patients may also lose large quantities of sodium and chloride through excessive sweating, copious sputum, draining sinuses, and large areas of denuded skin.

Increased sodium chloride intake is required by growing children, who deposit large quantities of these ions in bone. The need for sodium chloride is also great during lactation and in individuals exposed repeatedly to excessive heat.

The signs and symptoms of sodium chloride deficiency are: (1) dehydration and vascular collapse with a great reduction in total sodium chloride content; (2) muscular cramps with low sodium chloride concentration (see Chapter 57).

Sodium chloride deficiency must be differentiated from *chloride shift* in which hypochloremia, not hyponatremia, follows excessive carbon dioxide retention. This is seen in pulmonary disease

and cardiac failure with reduced vital capacity and impaired ventilation.

### POTASSIUM

Potassium is especially abundant in plant and animal tissue. It is the chief inorganic constituent of muscle and of most other tissue, very little being present in the fluid portions of the organism. Practically all foods of vegetable or animal origin contain several times as much potassium as sodium.

Potassium deficiency occurs most commonly in diarrheal disease in which depletion of this mineral follows large losses of intestinal secretion. Diarrheal disease of the newborn is an excellent example, and a great improvement in mortality rate has followed the use of potassium along with sodium and chloride in the treatment of this condition.

Potassium deficiency occurs with inanition. In this case, a negative potassium balance is due to tissue breakdown with subsequent excretion of potassium. In hospital patients given large quantities of glucose as their sole source of calories, serum potassium depletion may occur with considerable rapidity. Here one is confronted with chronic potassium depletion, complicated by an acute deficiency precipitated by the sudden withdrawal of potassium from the serum as glucose is deposited as glycogen.

Chronic potassium depletion or deficiency is associated with disturbance in the volume and concentration of electrolytes within the body cells. This gives rise primarily to nervous system symptoms of increased irritability, disorientation, etc. Sudden reduction of serum potassium, such as may occur during glucose infusion or in diabetic acidosis treated with large quantities of insulin, may be characterized by flaccid paralysis and cardiac abnormalities (see Chapter 59). There is a reciprocal relationship between sodium and potassium deficiencies, so that depletion of both cations appears to cause less derangement of function than does a similar depletion of one with a relatively normal or increased content of the other.

### PHOSPHATE

The most important dietary source of phosphate is milk and other protein foods. Phosphate deficiency may accompany potassium deficiency, and is particularly noteworthy in its consequent

impairment of carbohydrate metabolism. During glucose utilization, serum inorganic phosphorus is sharply reduced; inadequacy or deficiency of phosphorus may impair greatly carbohydrate utilization and insulin efficiency. Phosphate deficiency is also an important corollary of calcium deficiency in impaired bone formation.

### CALCIUM

The principal source of calcium in man's diet is milk and milk products. Calcium deficiency is most likely to occur during periods of greatly increased requirement—i.e., infancy, childhood, late pregnancy, and lactation. In intestinal disorders characterized by poor fat absorption, calcium may be lost in large quantities, (1) because of the formation of soaps and (2) because of associated deficiency in fat-soluble vitamins, particularly vitamin D.

Deficiency in total calcium is associated with osteomalacia. When calcium deficiency is accompanied by protein deficiency, osteoporosis is seen. Good bone formation requires that both protein and minerals be deposited in adequate quantities. Serum calcium deficiency gives rise to specific neuromuscular changes characterized by tetany. Hypocalcemia and hypophosphatemia are seen in diseases associated with deficient absorption of calcium; hypocalcemia and hyperphosphatemia occur in disorders in which calcium deficiency or shift is secondary to renal impairment, increased bone base, and phosphorus retention.

### MAGNESIUM

The principal sources of dietary magnesium are nuts, spices, meat, fish, and green vegetables, the amount in the latter being related to the chlorophyll content.

Magnesium deficiency is less well understood in the human, but appears to be associated in most instances with calcium and potassium deficiency. Deficiency of all three intracellular cations obviously will occur with inanition and increased tissue breakdown. Deficiency of all three of these cations also occurs in unregulated diabetes, in chronic renal insufficiency with polyuria and poor food intake, and in chronic diarrheal diseases. Although sodium chloride deficiency is readily appreciated in chronic diarrheal diseases such as ulcerative colitis, the possibility of associated calcium, potassium, and magnesium deficiency, at least the last two, is

rarely considered. Magnesium deficiency very likely leads to increased irritability of the central nervous system.

### IODINE

Iodine deficiency leads to goiter (see Chapter 55). It is common practice at present to attempt to supply adequate iodine in areas in which food is deficient in this element by iodizing the salt. The need for iodine during pregnancy is much increased, and many goiters may be prevented by the proper administration of iodine at this time and subsequently during lactation.

### IRON

Deficiency of iron is almost invariably due to insufficient intake or abnormal bleeding. In normal males there appears to be no appreciable excretion of iron. In females, the monthly menstrual flow permits large quantities of this element to escape from the body. Since milk is low in iron content, deficiency of this element frequently is observed in otherwise normal babies. Iron deficiency also occurs in conjunction with infections, in patients with prolonged menstrual bleeding, and in both males and females with acute or chronic blood loss. The characteristic cell of iron deficiency anemia is hypochromic, microcytic.

### TRACE ELEMENTS

In addition to the minerals which occur in large quantities within the body, a number of trace elements such as cobalt, zinc, and copper will be found in small quantities. It is thought that these elements participate as catalysts in a variety of important enzymatic processes. For instance, zinc is known to participate in the carbonic anhydrase system. The concentration of zinc in white blood cells is much higher than in tissues in general. It appears that cobalt must be available in the body in order that iron may be used for hemoglobin synthesis. Cobalt also exerts control over hemopoiesis; a deficiency of this element induces anemia, whereas an excess may produce polycythemia. Clinical symptoms representing clear-cut deficiencies of trace elements are not well established. Because of the chemical and physiologic importance of trace elements as catalysts of enzyme systems throughout the body, a deficiency of these elements may be associated with widespread impaired function,

although specific or pathognomonic changes may be difficult to detect.

### SUMMARY

In the world in general, undernutrition results primarily from inadequate food supply. In contrast to this, physicians in the United States will be confronted with nutritional deficiencies in patients with organic disease of the gastrointestinal tract; in systemic disorders, such as heart and kidney disease, which induce anorexia, nausea, and vomiting; in patients with psychologic and emotional difficulties (anorexia nervosa); and in patients who have been ill-advised regarding dietary regimes. Success in the treatment of undernutrition will depend, first, upon the ability of a patient to afford a nutritious diet and, second, upon the physician's ability to correct the disease process responsible for disturbance in food intake, digestion, absorption, and metabolism.

*Table 48*

#### RECOMMENDED DAILY DIETARY ALLOWANCES FOR AVERAGE ADULT\*

Milk.....	1 pint
Eggs.....	1
Meat, fish, poultry, or cheese.....	1 or more servings
Fruits.....	2 servings, 1 citrus or tomato
Vegetables.....	2 servings, green or yellow
Potato.....	1 serving
Cereal and bread, whole grain or enriched.....	4 servings
Cream.....	2 ounces
Butter.....	1 ounce
Dessert.....	1 serving
Other foods as needed to complete the meals.	

\* Food and Nutrition Board, National Research Council.

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# Obesity

George W. Thorn

General Considerations
Factors Relating to Emotional and Psychologic Difficulties
Low-Calorie-High-Protein Diet
Mineral Supplement
Vitamin Supplement
Laxatives
Exercise
Appetite Depressants
Metabolic Stimulants
Hormones
Maintenance after Reduction
Summary

## GENERAL CONSIDERATIONS

Obesity is a metabolic disorder characterized by the accumulation of excessive adipose tissue. It is usually generalized, but may be regional or localized. Obesity is an important disorder which is encountered with great frequency in countries or communities in which earning capacity is high and food production or availability exceeds caloric requirements. Obesity places a greatly increased burden on the heart, circulation, and weight-bearing joints. It is well known that serious disorders such as hypertension, heart disease, and diabetes mellitus occur with much greater frequency among obese individuals, and to some extent, at least, the course of these diseases may be ameliorated by correction of the accompanying obesity (see Chapter 59).

**Etiology.** The essential cause of obesity is the ingestion of food in excess of energy requirement. Normally there is a nice adjustment between appetite and caloric needs. When one considers the unlimited opportunity which free choice permits, it is amazing that so many individuals do maintain normal weight for so many years of their life. Self-selection diet studies have shown a remarkable capacity on the part of experimental animals and unconditioned infants to select a good diet containing adequate amounts of all dietary essentials. This capacity to select qualitatively essential food items is mediated by the taste buds. What regulates the quantity of foodstuffs ingested—in other words, what creates satiety—is less well understood. Evans suggests that satiety ensues when, following the ingestion of food, heat production attains a fixed per cent

increase over the organism's preexisting rate of heat production.

It has been known for years that lesions involving the hypothalamus may lead to obesity. Recently it has been observed that obesity may be induced experimentally by lesions, accurately placed with the Horsley-Clarke stereotactic apparatus, which involve the ventromedian nuclei of the hypothalamic tracts or tracts descending from them. Following the production of such lesions, there is an increase in body weight of 100 to 400 per cent, resulting primarily from a voracious appetite but accentuated by reduced activity and metabolic rate. The normal relationship between appetite and energy requirement is lost. Meal size and frequency of eating increase. Once a new plateau in weight has been attained, it remains quite constant. In rare instances, patients with brain injury or inflammation or tumor in and about the pituitary and hypothalamus develop a pathologic increase in appetite which is impossible to control except by the ingestion of tremendous quantities of food. It is probable that, in man, factors responsible for the nice adjustment between food intake and energy requirement may be mediated through the hypothalamus.

Excessive food intake may reflect family custom or conditioning; certain individuals derive great emotional satisfaction from the ingestion of food and may easily overindulge; many individuals are enabled to carry on excessive hours of sedentary work only by virtue of the "lift" derived from frequent snacks, particularly of foods high in carbohydrate, or from alcohol. Other patients accumulate excessive fat during convalescence from illness or injuries, particularly under circumstances which prevent normal activity. Many individuals with increasing age and reduced physical activity continue to ingest a diet which, at an earlier age with increased activity, merely met caloric needs. Any disorder which imposes reduced activity or results in a lowered metabolic rate will predispose a patient

to obesity unless a corresponding reduction is made in food consumption.

The essential cause of obesity is the ingestion of food in excess of energy requirement. *Obesity is not due primarily* to more complete absorption of food from the gastrointestinal tract, to hypometabolism, to lowered specific dynamic action of food, or to incapacity to mobilize fat stores. There may be considerable difference, however, from individual to individual with respect to the ease with which fat may be mobilized from fat depots during periods of dietary restriction. An important additional consideration is the rate at which carbohydrate may be derived from protein stores (gluconeogenesis). Familial predisposition to obesity may be inherited or may be the result of environment. In the latter case availability of food, eating habits, and customs, as well as emotional patterns, may play a dominant role.

Although obesity may be associated with several endocrine disorders, it rarely occurs as a direct result of hormonal deficiency. Obesity may develop either in the presence of or in the absence of the hypophysis, adrenal, thyroid, gonads, and islet cells of the pancreas. The secretions of the endocrine glands act more as the determinants of the distribution of fat deposition than as the cause of the deposition. It is possible that with certain hormonal disturbances fat reserves may not be mobilized so readily as in the normal; hence temporary hypoglycemia may develop, and, as a consequence, an increased food intake to combat hunger. Patients with Addison's disease or anterior hypophyseal deficiency, for example, despite reserves of fat and protein, are often unable to prevent hypoglycemia during short periods of starvation because of failure to mobilize sources of glucose and energy at a sufficiently rapid rate. In Cushing's syndrome (see p. 599), total body weight may not be appreciably increased, but there is increased deposition of adipose tissue in certain areas about the neck, waist and abdomen, the extremities remaining thin. Hyperinsulinism (see Chapter 60) is associated with obesity because of the attempt to counteract hypoglycemia by increased food intake. Patients with classic myxedema rarely are obese, although patients with less severe forms of hypothyroidism may gain weight excessively if food intake is maintained at normal in the presence of reduced energy requirement. It is essential to distinguish between hypometabolism and

hypothyroidism; they are not synonymous terms. Many endocrine disturbances *result from* rather than cause obesity. It is not unusual to note the onset of amenorrhea in a young girl who is gaining weight excessively, in whom simple caloric restriction with subsequent weight loss is followed by the resumption of normal menstrual periods.

**Pathology.** There is increased storage of fat in the subcutaneous tissue, in the retroperitoneal tissues, in the fascial planes between muscles, in the mediastinum, and about the organs, particularly the heart and kidney. In the lipodystrophies there is regional accumulation of fat, and in the lipomatoses abnormal fat deposits occur as discrete encapsulated masses.

**Clinical Picture.** Obesity may be asymptomatic or associated with a variety of signs and symptoms. The total mass of fat may lead directly to dyspnea on exertion, easy fatigability, and pain in the weight-bearing joints. Intolerance to heat, headache, sleeplessness, skin disorders, and digestive complaints are common. Indirectly, obesity may produce symptoms through the strain it places on the heart, kidney, and pancreas. Elevation of blood pressure and cardiac insufficiency, especially under physical stress; diabetes mellitus; and menstrual complaints are frequently observed.

**Diagnosis.** In most instances the diagnosis is obvious. Of greater difficulty is the establishment of *ideal* weight, and, hence, the degree of obesity. There is general agreement that body weight at any age should not exceed 10 per cent of the ideal weight at the age of 30 to 35. In the calculation of ideal weight, it is essential to consider the body frame (heavy, medium, light) as well as the height and sex (table 49).

**Treatment.** The only effective method of treating obesity is restriction of caloric intake below energy requirement. In so far as is possible, specific deficiencies are avoided by giving mineral and vitamin supplements in conjunction with a relatively high protein intake.

Dietary treatment should never be attempted prior to a thorough physical examination. It is also essential to understand the emotional and psychologic background of the patient. Successful weight reduction will depend upon sufficient motivation to permit long-continued caloric restriction with lifelong care and watchfulness. The physician must prescribe a dietary regimen suffi-

ciently individualistic to meet each patient's needs, and he must be willing to give the moral encouragement so necessary for a successful program.

Table 49\*

## IDEAL WEIGHTS FOR MEN (AGES 25 AND OVER)

Height (with Shoes)	Weight in Pounds (as Ordinarily Dressed)		
	Small Frame	Medium Frame	Large Frame
<i>Ft. In.</i>			
5 2.....	116-125	124-133	131-141
5 3.....	119-128	127-136	133-144
5 4.....	122-136	130-140	137-149
5 5.....	126-136	134-144	141-153
5 6.....	129-139	137-147	145-157
5 7.....	133-143	141-151	149-162
5 8.....	136-147	145-156	153-166
5 9.....	140-151	149-160	157-170
5 10.....	144-155	153-164	161-175
5 11.....	148-159	157-168	165-180
6 0.....	152-164	161-173	169-185
6 1.....	157-169	166-178	174-190
6 2.....	163-175	171-184	179-196
6 3.....	168-180	176-189	184-202

## IDEAL WEIGHTS FOR WOMEN (AGES 25 AND OVER)

Height (with Shoes)	Weight in Pounds (as Ordinarily Dressed)		
	Small Frame	Medium Frame	Large Frame
<i>Ft. In.</i>			
4 11.....	104-111	110-118	117-127
5 0.....	105-113	112-120	119-129
5 1.....	107-115	114-122	121-131
5 2.....	110-118	117-125	124-135
5 3.....	113-121	120-128	127-135
5 4.....	116-125	124-132	131-142
5 5.....	119-128	127-135	133-145
5 6.....	123-132	130-140	138-150
5 7.....	126-136	134-144	142-154
5 8.....	129-139	137-147	145-158
5 9.....	133-143	141-151	149-158
5 10.....	136-147	145-155	152-166
5 11.....	139-150	148-158	155-169

\* Metropolitan Life Insurance Company, Statistical Bureau, 1943.

Caloric restriction results immediately in an appreciable loss of energy and drive, which becomes less evident as the program progresses. Weight loss on a given caloric-deficient diet

proceeds more rapidly in the first weeks than later. This is due in part to the compensatory fall in basal metabolic level which always accompanies dietary restriction, and in part to loss of relatively large quantities of minerals and water. It is apparent that maintenance of a normal metabolic rate in the presence of inadequate caloric intake will result in more rapid weight loss than would occur spontaneously. Whether or not it is important or desirable to maintain an essentially normal metabolic rate is a problem which the physician must face. It is evident, however, that the fundamental problem is not changed, but that weight loss will be proportional to the caloric deficit in relation to the energy requirement. This difference may be increased by more stringent restriction of caloric intake or by increasing energy requirement, or both (see figure 92).

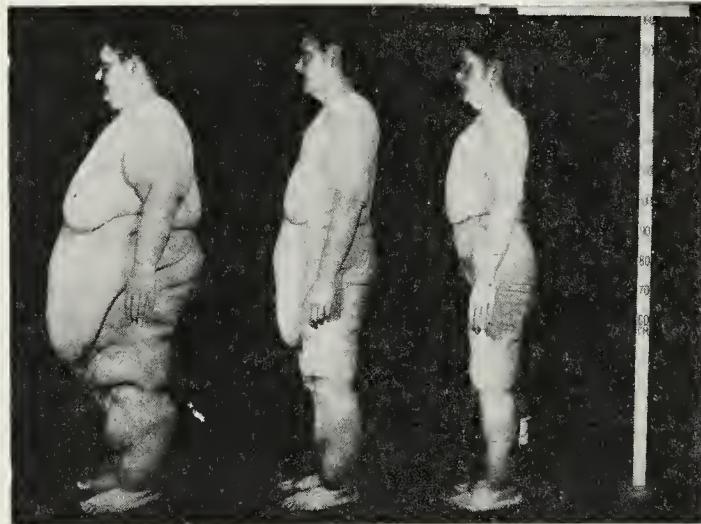


FIG. 92. Gradual weight reduction by diet alone in a 28-year-old female with obesity due to overeating. Excess subcutaneous and connective tissue had to be removed surgically after a loss of 120 pounds.

Because of the general depression which occurs during the first weeks of dieting, it is preferable to initiate the program in the spring, summer, or early fall, when climatic conditions decrease the incidence of respiratory infections. Substances such as "Benzedrine" have been advocated to overcome the depression or listlessness associated with dieting. Thyroid has been employed to prevent the normal compensatory fall in metabolic level, and substances such as "Dexedrine" find favor with many in an attempt to prevent the sensation of hunger. Unfortunately, all of these agents may have undesirable side effects if used excessively and may become somewhat habit-forming, to the ultimate detriment of the patient.

In female patients with an active ovarian cycle, it is helpful to point out the weight gain which normally occurs during the 10 days prior to the onset of menstruation. This is due to excessive retention of sodium, chloride, and water, and is much greater in quantity in obese individuals than in those of normal weight. Patients who maintain their diet carefully may be disappointed to observe no weight loss during the premenstrual period. This periodic retention of salt and water adjusts itself automatically by a subsequent diuresis and increased rate of weight loss at the end of the cycle. These cyclic changes may occur in the absence of menstruation in patients with active ovarian function.

Shifts in salt and water metabolism with changes in atmospheric temperature and humidity often induce relatively wide fluctuations in body weight from day to day. Because of this, it is often preferable for patients to weigh themselves only once weekly. This minimizes the effects of daily fluctuations and gives a truer picture of the actual over-all effect of the dietary regimen.

The fact that rapid shifts in body weight usually reflect alterations in salt and water intake or loss is taken advantage of by unscrupulous individuals who advertise "how to lose 12 pounds in 12 days!" Physicians may take advantage of the effect of salt restriction in encouraging patients temporarily, since this will, of course, greatly increase the rate of weight loss. The disappointment which follows the slower rate of loss after a week or so on this regimen usually offsets its psychologic advantage. Physiologically, there is little advantage, and indeed some danger, in restricting unnecessarily the intake of sodium chloride on a weight reduction program, unless edema or excess fluid retention is present. Under no circumstances should *water intake be restricted*, since dehydration is undesirable in a prolonged dietary regimen, and since edema is effectively controlled not by water restriction, but rather by sodium and chloride restriction (Chapter 28).

It is a relatively simple matter to estimate and adjust the caloric intake to desired weight loss in adults; it is a more delicate and difficult adjustment in children or in lactating or pregnant cases. Here it is essential not to deprive the body of essential building constituents. Under these conditions it is wise to effect weight loss at a relatively slower rate than in the adult, nonpregnant

patient and to provide maximum protein, vitamin, and mineral intake.

Weight reduction may be carried on safely at a more rapid rate between the ages of 20 and 50 than at either extreme. Elderly, moderately obese individuals who have maintained a relatively constant weight for many years should lose weight at a relatively slow rate. The ultimate advantage and possible improvement in physical condition with reduced weight should be considered in respect to the disturbance in equilibrium which is almost certain to ensue with dietary reduction.

### FACTORS RELATING TO EMOTIONAL AND PSYCHOLOGIC DIFFICULTIES

In no disorder is the prescription so simple and the possibility of cure so high as in the treatment of obesity. Why, then, is there so much discussion concerning the "best diet," such concerted effort to seek the "magic pill," such quackery and chicanery surrounding attempts to restore weight to normal? The answer is readily apparent: Dieting or caloric restriction maintained over any appreciable length of time requires courage and self-discipline of the highest order. To attain success a patient must possess sufficient motivation to enable him to carry through a prolonged program of relative starvation. This in itself may not be conducive to bodily comfort. Furthermore, if the ingestion of large quantities of food has provided certain emotional and psychologic satisfactions, the withdrawal may be accomplished only by substituting other "crutches" or, more properly, by increasing insight and understanding of the nature of the emotional disturbances and often subconscious conflicts which have formed a basis for the patient's present situation. In all of these considerations the physician's patience and understanding will be an important determining factor in the success of the program. There are a certain number of patients whose obesity has resulted from long-continued, modest excess of intake of calories over energy needs, due only to lack of information. For such as these it is a relatively simple matter to provide nutritional education and guidance. There is no deep underlying conflict, no overt disturbance in metabolism as the cause. The number of such cases is diminishing rapidly as the appreciation of the dangers and difficulties

which confront the obese individual becomes more widespread.

**Motivation.** In general, motivation sufficient to permit a patient to follow the diet prescription arises from one or more of the following factors:

1. Pride in personal appearance.
2. Symptoms of disordered physical function (shortness of breath, painful knees).
3. Fear of future disease (diabetes).
4. An attempt to avoid the antagonistic reaction or "pressure" manifested by friends, relatives, or business associates.

Obviously the last is the least satisfactory and, if at all potent, almost invariably leads to resentment. The danger in this instance is intensified by the probability that disturbed interpersonal relationships with mother, father, sister, or employer may have played an important role originally in the genesis of obesity. The submission to authority or will under these circumstances, while occasionally successful in accomplishing the immediate end (weight loss), may result in the development of much more serious emotional conflicts.

A good example of this type of situation is the obese young girl "led" into the physician's office by an "understanding" but directive mother. Under these circumstances the chance of long-range, permanent improvement is poor. In contrast, picture the same young woman, realizing the necessity for weight reduction in order to increase her personal attractiveness and opportunity for social engagements. It is apparent at once that obesity prior to or accompanying adolescence is extremely difficult to control, whereas postadolescent girls may develop adequate motivation which ensures success of the regimen.

Although the presence of organic disease or the fear of its development may provide strong motivation for weight reduction, it must be appreciated that these same patients may have used the satisfaction derived from food as an important aid in meeting life's problems. The conflict which arises when dietary restriction becomes necessary should be fully appreciated. On the one hand, there is fear of the consequence if weight is not reduced; on the other, the patient may be faced with the loss of an important source of satisfaction. In some individuals who are incapable of making a reasonable, healthy adjust-

ment to this predicament, the long-range effect of diet restriction may exert a detrimental effect on the underlying disease despite immediate benefits associated with weight loss.

Obese patients will vary greatly in the ease with which moderate dietary restriction enables them to lose weight. Some patients will lose satisfactorily on diets of 1500 to 1800 calories; others must be restricted to 600 to 800 calories. The inconvenience involved as well as the fortitude required to follow the very low-caloric diets is great. It is important for the physician to weigh motivation against the dietary program. Thus, in instances in which only moderate restriction is necessary, success is almost certain with reasonable motivation; whereas patients requiring severe caloric restriction for prolonged periods will need the strongest motivation. The skill with which the physician is able, on the one hand, to estimate the degree of dietary restriction which will be necessary and, on the other, to match the forces conspiring to motivate the patient will determine his success or failure in a therapeutic program.

From a psychologic and emotional viewpoint, it is important and helpful for a physician to attempt to determine whether in a given case it is possible and desirable for a patient to continue on an unbroken restricted program for a prolonged period; whether an individual patient will do better with more rigid general restriction of calories than is necessary, but thereby permitting a few special items of particular desirability to be included; or whether a certain patient is unable to maintain rigid restriction for a prolonged period but is able to maintain rigid restriction for a definite period followed by a short period of "relapse" or "relief." Over a period of months the same end may be attained by several pathways.

Again it is necessary to emphasize that a diet prescription is a relatively simple procedure, but that a thorough understanding of the factors contributing to obesity will require a real expenditure of time, effort, and understanding. And, finally, a dietary program should not be undertaken unless a physician is certain that over-all improvement is possible. One is hardly justified in attaining immediate gains at the risk of inducing long-range difficulties. It must be apparent at this point that the "aura" which surrounds many diet fads and programs is a conscious or

unconscious attempt to increase, improve, or fortify the forces necessary to create adequate motivation. One of the important aspects of the "cults" and "spas" is the reinforcement of motivation associated with constant supervision and the force exerted by group enterprise. Very often interest, pride, and cooperation are stimulated by the discussion and exchange of ideas which occur in conjunction with "classes" or "groups" of patients on a similar regimen. The desirability and value of discussing personal problems which may have arisen in conjunction with the application of the dietary program are apparent. For ultimate and permanent success, however, the individual must not become too dependent on the group. A physician in private practice may thus strengthen motivation by planning to have certain of his patients on weight-reducing programs meet in his office in a group. This also offers the possibility of providing dietary instruction more efficiently. It is important to recognize the fact that during the first few days or weeks on reduced food intake there is almost invariably some degree of physical weakness and incapacity. During this period it is desirable for the physician to see his patients more frequently. Explanation and reassurance at this time are invaluable.

#### LOW-CALORIE-HIGH-PROTEIN DIET

There is universal agreement that, in addition to caloric restriction, it is desirable to maintain a relatively high protein intake. Such a regimen reduces the negative nitrogen balance and prevents specific amino acid deficiencies which are more likely to occur in the presence of caloric-deficient diets. A high-protein diet takes advantage of the specific dynamic action of protein, preventing, to some extent, the fall in metabolic rate which follows restriction of caloric intake. An adequate protein intake assists in maintaining a more constant blood sugar level, thus avoiding the relative hyperglycemia immediately after a predominantly carbohydrate meal and the relative "hypoglycemia" two to three hours later. Protein foods have increased "satiety" value. This, no doubt, is due, in part at least, to the increased specific dynamic action of proteins and the facilitating of gluconeogenesis.

The importance of the "satiety" value of protein and its beneficial effect on blood glucose levels is intensified by the concomitant low fat

content of low caloric values. Fat provides 9 calories per gram in contrast to protein and carbohydrate, from which only 4 calories per gram are derived. Fat delays, to some extent, absorption of carbohydrate from the intestinal tract, thereby preventing the wide swings in glucose level which accompany a diet composed largely of carbohydrates. In the absence of dietary fat, the dietary protein content assumes greater importance in these respects.

It is estimated that the utilization of 100 Gm. of glucose in the presence of adequate calories will prevent significant acidosis or excessive ketone and fatty acid formation and utilization. Acidosis in patients with diet restriction will vary with the relative reduction of calories in respect to energy requirement and with the relative proportion of dietary carbohydrate, protein, and fat. A relatively high-carbohydrate and high-protein diet will minimize the degree of acidosis and negative nitrogen balance.

In estimating the caloric content of a reducing diet, it is essential to evaluate the patient's overall activities and energy requirement as well as his normal dietary intake (total caloric content and constituents). It is also important to consider his likes and dislikes and to plan a diet which will provide a maximum content of essential constituents (amino acids, minerals, and vitamins) with a minimum of caloric content.

In almost all instances it is desirable to accomplish weight loss gradually rather than suddenly. A slow rate of weight loss allows better adjustment on the part of the body and is a protection against more serious deficiencies. There is opportunity for tissue to regain some of its elasticity, and the psychic and physical disturbances which occur with redundant folds of skin may be prevented. Weight reduction should certainly proceed at a slow rate in the elderly, in the very young, and in pregnancy and lactation.

**Total Calories.** In approaching this problem the physician must be empirical. Every patient is anxious to attain his ideal weight at the earliest possible moment. It is essential for the physician to decide the rate of weight loss which is most desirable for an individual patient. He must not be influenced unduly by his patient's demands. He must explain the necessity for relatively slow rate of weight loss and emphasize the attitude that a great weight loss may be accomplished over a prolonged period by moderate methods.

and that undue dietary restriction may be fraught with real dangers to health.

A simple initial step for the average middle-aged male or female patient is the prescription of a diet constituting 1000 to 1500 calories, depending upon the general activities of the individual. Such a diet presents no serious problem at home or in most restaurants. Its cost will be relatively high because of the desirability of obtaining as high a protein content as possible, 80 to 120 Gm. The more obese the individual, the greater the restriction of calories. The diet is advantageously administered with some allowance for intermediate feedings at 11:00 a.m., at 4:30 p.m., and at bedtime. It is helpful to prevent undue hunger by this means.

Weight loss in most instances should not exceed 1 to 2 pounds per week after the first two weeks. Total caloric intake should be adjusted to this, with the realization that on a given diet one may expect more rapid weight loss in the beginning; that patients with cardiac insufficiency may lose large quantities of salt and water which should not be interpreted as tissue loss; that very obese individuals may lose safely at a greater rate than this; and that growing children should lose more slowly than this.

Most patients with moderate activity will lose satisfactorily on a 1200- to 1500-calorie intake. Some patients may have to be restricted to 1000 calories or less. There is no real justification for diets under 800 calories for ambulatory patients. Failure to lose weight on a diet prescription of 800 to 1000 calories almost invariably means that the diet formula has been misunderstood or is not being followed. For short periods of time a diet of 500 to 600 calories may be given, but the potential dangers of such rigid restriction should be appreciated. Furthermore, since life-long attention must be given this problem by the patient, it is more important for the physician to spend his time in helping to develop a proper attitude than in "micro-dissecting" the diet calorie by calorie. The establishment of fads, phobias, and fancies is to be avoided at all cost. The patient should appreciate that his diet may be the same as any normal individual. With the exception of high protein content it is necessary only to reduce the total quantity of food. He will learn that there are certain advantages in rearranging his diet for his own comfort and convenience, but that the essential

requisite is only one—*limitation of calories below energy requirement*.

Many excellent articles have been written with a view toward helping the physician and patient attain this end. In these discussions the advantages of bulk, the satiation value of foods high in protein, and the preparation of tasty foods of low caloric value are discussed at length. The means by which the diet is manipulated should not be confused with the end, which is only caloric restriction with the preservation of optimum essential food constituents.

*Of great help to physician and patient during the early period of dietary regulation is the maintenance of a diary in which the patient writes down each article of food which he eats along with the approximate quantity. This should be checked over carefully by physician and patient together. Such a record is invaluable in suggesting necessary changes in diet, in rearranging meals and feedings, and in providing a simple means of detecting errors of omission as well as commission.* Patients should know that it is vital for their good health that they abide by the restrictions imposed but that they also eat all of the diet which they are permitted.

## MINERAL SUPPLEMENT

Only three mineral replacements need to be considered—calcium, iron, and iodine. The indication for all three is great during periods of growth and pregnancy. Because large amounts of skimmed milk are permissible on most weight reduction diets, it is not necessary to provide additional calcium unless the patient is unable to drink milk. In this instance it is wise to give calcium lactate or calcium gluconate, 0.3 Gm. three times daily. Iron need not be given except in growing children or in pregnancy, unless anemia is present. In patients with anemia, iron should be employed in conjunction with a high protein intake. Ferrous salts are preferable; ferrous gluconate may be given in doses of 0.3 Gm. three times daily.

Iodine is particularly necessary as a supplement in growing children and during pregnancy. Supplementary iodine may be obtained most easily by using iodized salt. As the total content of food is reduced, it is often necessary to be certain that the content of iodine is adequate, particularly in areas in which iodine deficiency exists.

### VITAMIN SUPPLEMENT

Emphasis should be placed on a well-rounded, nutritious diet, since there may be essential factors of which we are not now cognizant. In addition, it is wise to provide an adequate supplement of the known vitamins. This is most easily accomplished by giving one or two of the readily available multivitamin tablets. The National Research Council standards of adequate intake are given in Chapter 41, table 48.

### LAXATIVES

Most patients will become constipated on weight-reducing programs because of the low fat content of the diet. As a consequence of this, hemorrhoids are likely to develop. Mineral oil at night is very helpful; the dose may be adjusted to individual needs, one to three tablespoonfuls usually being adequate. Bulky foods in the diet also may prove helpful.

### EXERCISE

Increased physical exercise is excellent for improving general health and body "tone" in those individuals without serious organic disease. Patients should be instructed, however, that it requires a great deal of exercise to assist appreciably in weight loss. Thus, if food intake is held constant (and this may present difficulties with increased exercise), playing 18 holes of golf may utilize 800 to 1000 calories. Exercise is helpful, and its value should not be underestimated, but the quantitative aspects should be carefully discussed with each patient.

Physiotherapeutic measures are useful in obese individuals with and without circulatory difficulties. Such measures increase tone and help in the redistribution of fat. They do not remove fat, although they may assist in its distribution. Physiotherapeutic measures also assist by increasing and improving the elasticity of the tissues.

### APPETITE DEPRESSANTS

A variety of substances such as ipecac, digitalis, and "Benzedrine" have been proposed as aids in weight reduction by inhibiting or decreasing appetite. For some patients such substances prove quite helpful, particularly in the early weeks of the restricted food intake. It must be ascertained that such substances exert no deleterious effect on the body in general; and it

must be recognized that the patient on insufficient calories is relatively more vulnerable to the effect of noxious agents.

### METABOLIC STIMULANTS

Repeated efforts have been made to discover a nontoxic agent which would maintain a normal metabolic level in the face of weight loss. Dinitrophenol has had the widest use. The consensus today is that its undesirable toxic side reactions make its use unjustified.

In most instances, substances of this type are being employed by physicians or patients in an attempt to induce *weight loss without caloric restriction*. To do this, it is obviously necessary to raise basal metabolic level *above normal*. There is no known substance which can be used safely to increase metabolic level above normal for prolonged periods of time without danger of toxicity.

Other drugs have been employed in an attempt to offset the fatigue which is so common early in a weight reduction program. There is no harm in using such stimulants as caffeine or "Benzedrine" in small doses for a limited period of time. It is not necessary to use these substances in most patients, however, when the caloric reduction is moderate, and the dangers of habituation and untoward effects of these drugs should be carefully considered before being recommended.

### HORMONES

In the mind of the lay public, "hormones" are the most important cause of obesity and are hopefully considered to be its cure. The well-informed physician recognizes to what a small extent disturbances in hormone secretion are primarily responsible for obesity and how futile most types of hormone therapy are as cures of obesity.

No pituitary preparation now available is useful in weight reduction. Certainly preparations of male and female gonadal hormones and adrenal extracts have no place. Thyroid therapy has received wide application and merits special discussion.

Thyroid therapy is effective substitution therapy in patients with hypothyroidism. Unfortunately, however, the number of patients with hypothyroidism among the obese is relatively small. Thyroid therapy has a definite and permanent effect on the metabolism of the hypothyroid case. Complete thyroid deficiency may

require 0.2 Gm. of thyroid (U.S.P.) daily; 0.1 Gm. of thyroid (U.S.P.) daily should be adequate for milder cases. A given dose of thyroid will produce a predictable rise in basal metabolic rate in a patient with hypothyroidism, and a daily dose of thyroid will maintain the increase in basal metabolic rate indefinitely. Unfortunately, in the minds of many physicians as well as patients, the term *hypometabolism* is synonymous with *hypothyroidism*. This readily leads to confusion and to the unwise and unwarranted administration of thyroid extract. In fact, it might be stated conservatively that at least 75 per cent of patients now taking thyroid extract do not need it.

When thyroid extract is used to increase the metabolic rate of a patient with hypometabolism rather than hypothyroidism, it is being used as a pharmacologic agent. With the initial dose of thyroid some increase in basal metabolic rate will occur, since the total circulating thyroid present in the body will be increased temporarily. Since the thyroid gland is functioning in this patient, however, the continued administration of thyroid extract will exert a depressing effect on the gland, and before long the patient will have returned to the same level of circulating thyroid as he had prior to medication, the only difference being that he is now purchasing one half or two thirds of his thyroid hormone. Since the patient was stimulated by the first increment and since that effect appears to have worn off, the physician and the patient agree to increase the dose again, and the same cycle ensues. With each increment there is temporary stimulation of metabolism with a subsequent fall, until the total dose of thyroid exceeds that which the gland normally puts out, and persistent signs of hyperthyroidism become evident.

If such a patient on thyroid extract is seen by a skeptical physician, it is extremely difficult to persuade the patient that he does not need thyroid. First of all, he states that he *did feel better when thyroid was first given!* Second, if the thyroid medication is discontinued, the patient will almost certainly experience a marked fall in basal metabolic rate and will develop signs and symptoms of hypothyroidism which may be expected to persist for several weeks or months, until the thyroid gland is again normally stimulated to activity. It requires the utmost coöperation for a patient to undergo such a procedure, as he will

most certainly tend to gain weight during the period of temporary hypothyroidism. It is easy to see why patients once started on thyroid extract may continue it unnecessarily for years.

### MAINTENANCE AFTER REDUCTION

Patients should understand thoroughly when they undertake a reduction diet that, in all probability, some degree of dietary restriction or discretion will be necessary permanently after ideal weight has been attained. The degree of dietary restriction is best attained by establishing the custom of weighing in each morning and adjusting the day's intake of food to the changes in body weight. It may be necessary at this time for the physician to review the comparative caloric content of certain foods which may have been withheld during the diet regimen. It is usually desirable to discuss in detail the calories contained in alcoholic beverages.

Once ideal weight has been attained, a patient should be encouraged to visit his physician every three to six months for examination and advice. The continued interest of the physician is of paramount importance to the health and happiness of his patient.

### SUMMARY

In actual practice the successful regulation of most patients with obesity will depend upon a thorough knowledge of the fundamentals of dietetics on the part of the patient, and upon a comprehensive understanding of the patient by the physician. Weight loss will occur only if caloric intake is reduced below energy requirement. Ninety per cent of the popular discussions about weight-reducing regimens are concerned with means which attempt to defy the second law of thermodynamics!

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## Ascorbic Acid Deficiency (Scurvy)

William J. Darby

**Definition**  
**Etiology**  
**Pathologic Changes**  
**Physiologic Considerations**  
**Clinical Findings**  
**Diagnosis**  
**Therapy**

**Definition.** Scurvy is a deficiency disease resulting from a lack of ascorbic acid. It is characterized by failure of deposition of intercellular substances such as collagen, osteoid, and dentine. This results in hemorrhagic manifestations and changes in the bones and joints.

**Etiology.** It is universally accepted that vitamin C deficiency is the cause of scurvy. In general, this deficiency is of dietary origin, although, in the occasional scorbutic patient, conditioning factors may be present. The more common conditioning diseases are those characterized by chronic diarrhea or steatorrhea, or those which may result in restriction of dietary intake, such as in peptic ulcer or psychiatric aberrations.

Dependable dietary sources of vitamin C are fruits (especially citrus), green leafy vegetables, raw vegetables, Irish potatoes, and tomatoes. Unheated (raw) milk contains some ascorbic acid and, when consumed in large quantities, may contribute materially to the diet. The vitamin C content of milk is reduced during the process of pasteurization, evaporation, and the like. The cooking or processing of foodstuffs usually results in decrease in vitamin C content.

A dietary deficiency of ascorbic acid may occur in infants due to failure to supplement a milk formula with sources of ascorbic acid. In the adult, scurvy is encountered most frequently in individuals who live alone, do little cooking, and for one reason or another consume a diet devoid of those foods enumerated above. The subjects are oftentimes bachelors or widowers. In fact, the term "bachelor's scurvy" has been coined to apply to the disease occurring in this group. In most series, men predominate and the largest numbers usually occur in the older age groups. Sex does not appear to be a factor in infantile scurvy. Scurvy is rare in the breast-fed infant.

In summary, scurvy is a disease most likely to be encountered in artificially fed infants less than a year old, and in adults in the older age groups, particularly men who live alone and with meager economic resources.

There exists no peculiar geographic pattern for scurvy which cannot be correlated with the regional dietary pattern. When epidemics of scurvy appear, investigation reveals that for one reason or another the population has been deprived of a usual source of ascorbic acid.

**Pathologic Changes.** Most students of scurvy are agreed that the fundamental pathologic lesion is the failure of deposition of collagen, osteoid, or dentine by the respective cells—the fibroblasts, osteoblasts, or odontoblasts. This fundamental defect in the formation of intercellular substances explains numerous observations. Thus, impaired wound healing in the vitamin C-depleted organism is associated with lack of collagen formation at the site of the wound. Excellent illustrations of this in experimental scurvy are to be found in the appended References. Associated with the failure of collagen formation in wounds is failure of capillary loops to invade the injured area. These defects in the scorbutic person may impair the healing process in tissue injury other than operative wounds.

Hemorrhage is a striking manifestation and may occur from almost any organ. The less severe degree is manifest as petechiae at sites of trauma. In the infant, the diaper region is the usual location. In the adult, the petechiae occur first below the knees. In the adult, these early petechiae are perifollicular. In more severe cases, the hemorrhage may be manifest as widespread ecchymotic areas, or hematomas (particularly subperiosteal hematomas in infants). Hemorrhages into the joint are not infrequent in severe scurvy.

Gingival swellings, livid red in character and bleeding on slightest trauma, occur in moderately severe to severe scurvy. Initially, the interdental papillae become swollen, red, and friable. In

severe cases the teeth may loosen and secondary infection of gingivae may occur. The gum lesions do not appear in edentulous individuals.

Changes in bony structures are most pronounced in infants and may include subperiosteal hemorrhage, "beading" of the ribs at the costochondral junction, and increased fragility of the bones. Microscopically, these bone lesions are characterized by a failure of ossification of the calcified matrix.

**Physiologic Considerations.** Ascorbic acid is easily oxidized and thereby readily inactivated by heat in the presence of oxygen. A variable loss of the substance occurs during the processing of food and in aqueous solutions upon standing. The vitamin is rapidly absorbed from the gastrointestinal tract, except in most extreme conditions of gastrointestinal tract disease. The development of scurvy in the adult requires some four or five months of depletion. Ascorbic acid is excreted by glomerular filtration and active tubular reabsorption. There is a maximal rate of tubular resorption, so that when the vitamin is presented to the tubules at a rate exceeding this maximum the excess is lost in the urine. The renal threshold for vitamin C is placed at a plasma concentration of somewhat above 1 mg. per 100 ml. This, however, varies considerably from individual to individual. Nevertheless, there is a ready loss in the urine of ascorbic acid administered in excess of that required to saturate the tissues and meet the day-to-day needs of the individual.

The role of ascorbic acid in the formation of intercellular substance has been discussed. The other well-confirmed metabolic role of this vitamin is that it enables the organism to metabolize large quantities of the aromatic amino acids, tyrosine and phenylalanine. In the premature infant with low ascorbic acid stores, but without evidence of clinical scurvy, the administration of added aromatic amino acids is followed by a high urinary excretion of the intermediary metabolites, *p*-hydroxyphenylactic and *p*-hydroxyphenylpyruvic acids. Similarly, in infantile and adult scurvy, a load test of tyrosine is followed by the excretion of these intermediary metabolic products. This metabolic defect serves, therefore, as an indicator of functional impairment due to vitamin C deficiency. Accordingly, the nonscorbutic premature infant may be con-

sidered to be in a state of potential deficiency disease.

Serum or plasma levels of ascorbic acid above 0.6 mg. per 100 ml. are usually associated with the zone of saturation. Plasma levels seldom exceed the renal threshold. Concentrations in the plasma ranging from 0.0 to 0.6 mg. per 100 ml., while usually indicative of unsaturation may be consistent with health. Untreated scurvy is not encountered in the presence of detectable quantities of ascorbic acid in the plasma (or serum).

The level of ascorbic acid in the plasma is a reasonably dependable indicator of the magnitude of the recent vitamin C intake. A pronounced depression in plasma ascorbic acid occurs within three weeks after removal of the vitamin from the diet, and the concentration falls to zero within six to eight weeks.

**Clinical Findings.** The infant with scurvy is a somewhat anxious, slightly pale baby, usually 5 to 12 months of age. The position is characteristic: the child lies on his back with one or both thighs slightly flexed and abducted to assume the so-called "frog position." He generally cries as the bed is approached and shows evidence of exquisite tenderness and swelling of one or the other, or both, knee or ankle joints. Petechiae may be present, particularly in the diaper region or other areas subject to trauma. If dentition is present, the gums around the erupted teeth may be swollen and red, and bleed on slight pressure. "Beading" of the costochondral margins is usual.

Roentgenologic examination of the lower femur of the scorbutic infant may reveal evidence of subperiosteal hemorrhage. This coincides with the usual site of painful swelling. Other x-ray signs include irregular-appearing bands and separation of epiphyses (especially at the lower end of the femur, the upper end of the tibia, the head of the humerus, and the costochondral junctions). In addition, there may be found the characteristic white line of Fraenkel—a white, transverse, somewhat irregular band most often seen at the lower end of the radius or femur.

In the adult the appearance of signs of the disease is usually preceded by a period of lassitude, some anorexia, and vague muscular aching, followed by the development of perifollicular hemorrhages of the lower extremities. Petechiae appear and may become larger and coalesce in some areas; ecchymoses, and even hematomas, develop in severe cases. Unless the patient is

edentulous, he usually develops swollen, red-to-bluish, hypertrophied, friable gums. These bleed either spontaneously or readily upon light pressure.

If anemia occurs in the scorbutic infant, it is not generally regarded as a manifestation of the vitamin C deficiency itself. Some scorbutic infants exhibit a hypochromic microcytic anemia of iron deficiency; others show a megaloblastic anemia which responds to folic acid. In most babies with scurvy, however, anemia is not noteworthy. In the scorbutic adult, however, from 30 to 90 per cent of the patients exhibit appreciable degrees of anemia, normochromic and normocytic or slightly macrocytic in character. In hospitalized patients the anemia seems to disappear slowly and without appreciable reticulocytosis, following the treatment of the disease with ascorbic acid. The exact relationship between the anemia and ascorbic acid deficiency is debated. The anemia may, in some cases, be a manifestation of a deficiency of one of the hemopoietic vitamins; in other instances, it may be due to concomitant iron deficiency; and, in still other patients, it is possible that it is a manifestation of ascorbic acid deficiency per se.

**Diagnosis.** The diagnosis of scurvy can be established by the combination of a carefully obtained dietary history, disease history, physical examination, and certain laboratory and, in infants, x-ray studies. Laboratory studies of value include fasting plasma ascorbic acid coupled with one or another of the load tests. In infants, the procedure developed by Kajdi is very useful. A fasting plasma level is determined, followed by a second observation four hours after the intramuscular injection of a 200 mg. test dose. A four-hour rise to less than 0.2 mg. % is good evidence of scurvy. A rise to less than 0.6 mg. % is evidence of definite unsaturation of ascorbic acid. A similar test is of value for adults, but perhaps a more convenient one consists of the oral administration of 15 mg. of ascorbic acid per kilogram of body weight and the determination of the plasma level at two, three, four, and five hours. In the clinically manifest scorbutic, the maximum rise is rarely greater than 0.4 mg. %.

Tyrosine load tests have not as yet been standardized, but may promise even more precise diagnostic aid. The determination of ascorbic acid concentration of the white cell-platelet layer is a helpful technic but, because of its technical difficulties, is not available ordinarily for clinical use.

**Therapy.** It has been demonstrated repeatedly that saturation of the tissues of the adult scorbutic subject requires between 3 and 4 Gm. of vitamin C. Accordingly, it is not unreasonable to attempt to provide such amounts of vitamin C to the scorbutic patient within a relatively brief period of time. This may be done by administration of oral doses of ascorbic acid in amounts of 300 to 1000 mg. daily for 4 to 10 days. Additional supplementary therapy with ascorbic acid is unnecessary, provided dietary correction is introduced. As with all deficiency diseases, permanent cure is obtained only by correction of the poor dietary pattern which led to the development of the disease.

The prevention of ascorbic acid deficiency lies in the early addition of dietary sources of vitamin C to the diet of infants and, in adults, education and the institution of social measures designed to eliminate those conditions which contribute to scorbutigenic dietary patterns.

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# 44

## Nicotinic Acid Deficiency (Pellagra)

William J. Darby

Definition  
Etiology and Pathogenesis  
Incidence and Epidemiology  
Pathologic Findings  
Clinical Findings  
Laboratory Findings  
Diagnosis  
Treatment  
Prognosis

**Definition.** Pellagra is a deficiency syndrome characterized by dermatitis (usually symmetric lesions of exposed surfaces), glossitis and stomatitis, diarrhea, and, in later stages, dementia.

**Etiology and Pathogenesis.** Pellagra may occur as a result of a dietary deficiency or be conditioned by other diseases, particularly those of the gastrointestinal tract.

The typical pellagragenic diet has been described as consisting of the three M's—(corn) meal, (fat) meat, and molasses. The fat meat is the salt pork or "side meat" which contains almost no lean. While this is a slight oversimplification of the dietary pattern characteristic of pellagrins, it does illustrate the outstanding attributes of the diet upon which the syndrome develops—namely, a monotonously restricted diet including almost no green leafy vegetables, and very poor in sources of animal protein, milk, and other dairy products. Finally, in most regions in which pellagra is common, corn is a staple dietary constituent, and corn bread may account for from 40 to 60 or more per cent of the total caloric intake of the pellagrin.

Such pellagragenic diets are relatively low in, though not devoid of, niacin, and seem to contain scanty amounts of the amino acid tryptophane. It is now clear that tryptophane may serve as a precursor of niacin in the body, so it seems justifiable to conclude that in order for pellagra to occur there must exist a deficiency of both niacin and tryptophane.

It has long been held that corn contains a toxic pellagragenic factor. Unconfirmed evidence from animal studies supports such a view. On the other hand, it is not essential under all circumstances that corn be included in the human diet

in order that pellagra occur. For example, pellagra was noted in prisoners of war in the Philippines during World War II, despite the absence of corn from the diet. It is of considerable interest that under these circumstances nutritional edema was universal.

When pellagra was epidemic in the southern United States, it was marked by a definite seasonal incidence. The peak of the pellagra season occurred in May, June, and July, and the incidence decreased during the latter part of the summer to reach the lowest points during the winter months. The curve of the incidence of pellagra parallels remarkably the seasonal variation in intensity of the sunlight. It has been demonstrated clearly that the dermatitis of exposed surfaces is precipitated in pellagrins by exposure to the sun.

In summary, then, pellagra may be thought of as the syndrome which results from exposure to the sun of the niacin- and protein (tryptophane)-depleted subject. Manifestations of a deficiency of other B vitamins may frequently coexist.

Secondary or conditioned pellagra has been related to a multitude of associated diseases, including diseases of the alimentary canal, hepatic disease, surgical procedures, infections, pregnancy and lactation, neoplastic disease, and so forth. References which provide a detailed listing and discussion of these are appended.

Alcoholic pellagra is no different from the usual disease except that, etiologically, alcohol has displaced other foods to such a degree that the subject becomes depleted of pellagra-preventive factor(s).

**Incidence and Epidemiology.** It appears that sporadic cases of pellagra occur throughout the world. Areas in which epidemics have occurred include the southern United States, Transcaucasia, Bulgaria, Rumania, Spain, Africa, Chile, Egypt, and India. In the last two decades the florid disease has disappeared almost completely from the southern United States. For example, in 1928, 6969 deaths were reported from the

registration area, while in 1946 only 804 deaths were attributed to pellagra. This decrease in pellagra in the United States has been continuous since the early 1930's and is most logically to be attributed to a great many factors, including educational efforts directed toward improving agricultural practices, food preparation, conservation, and dietary habits; improved economic position of the poorer groups in the population; increased availability to the economically underprivileged of a wide variety of wholesome processed foods; the decrease in area isolation due to better systems of communication and travel; the gradual change from the one-crop system of farming; and the industrialization of many regions.

**Pathologic Findings.** The pathologic findings in pellagra are not specific. The tissues involved include skin, mucosal surfaces, gastrointestinal tract, nervous system, and, in some instances, blood.

It has been indicated that the initial skin change ascribable to nicotinic acid deficiency is rarefaction of the corium and dilatation of the blood vessels. Simultaneously occurring epithelial changes include hyperkeratosis, parakeratosis, and acanthosis. Bullae are attributed to separation of the epidermis due to the changes in the corium. Later the superficial layers of the epidermis and the sebaceous glands become atrophic.

The mucosal surfaces—mouth, esophagus, vagina—exhibit similar dilatation of blood vessels and epithelial atrophy. Ulcerations of the mucosa may develop. The epithelium of the colon may be atrophic, and the walls thickened and inflamed, exhibiting cysts or ulcerations characterized by fibrin formation and collections of inflammatory cells. The relationship of these colonic lesions to nicotinic acid deficiency is not clearly established, and it has been noted that they are quite similar to the changes observed in pantothenic acid-deficient swine.

Anemia is inconstantly associated with pellagra and may be microcytic or macrocytic. In either case, it would appear to be a manifestation of another deficiency disease—in the former instance, iron deficiency; in the latter, a deficiency of the newer hemopoietic vitamins (folic acid, B<sub>12</sub>).

The angular fissures and "magenta tongue" may, on occasion, be signs of ariboflavinosis. The

ocular lesions of ariboflavinosis may also be noted in pellagra.

Fatty infiltration of the liver has been described in pellagra and emphasized particularly in the disease as seen in Africa. This finding is most likely a manifestation of a deficiency of lipotropic substances rather than of nicotinic acid.

The lesions described as occurring in the nervous system are quite variable and nonspecific.

It is obvious that the syndrome of pellagra represents, in the main, a deficiency of niacin which may be associated with the findings of any of a number of other deficiency states. This view readily explains the variable pathologic and clinical picture of the disease.

**Clinical Findings.** It is now rare to find a "typical pellagrin" who exhibits all of the manifestations of the disease. However, the pellagrin usually has experienced lassitude, anorexia, rather vague digestive symptoms, and emotional instability described by the patient as "nervousness" for some weeks. Following a few days of work in the field (exposure to sun), the patient notes some burning and stinging of the hands, face, and neck, and within a day or so there has appeared a fiery red erythema which is interpreted as sunburn by the patient. Vesiculation progressing to bullous lesions appears on the backs of the hands and sometimes on the face and neck. When seen by the physician the bullae may have been opened or may have ruptured spontaneously. In some instances they become secondarily infected. Soreness of the tongue and mouth and symptoms of vaginitis may develop in association with the erythematous changes. The development of the acute phase of the disease is accompanied by diarrhea and increased anorexia.

The initial relatively mild nervous manifestations of headache, irritability, insomnia, and burning of the hands and feet give way in the acute pellagrin to definite personality changes. These patients appear to react slowly, to be uninterested, and to be mildly to completely disoriented, and exhibit hallucinations and delusions. The mental symptoms at times so dominate the picture that pellagrins have been referred to mental institutions before the correct diagnosis became apparent.

On occasion the history may further reveal that the patient has experienced in previous years one or more somewhat similar, but less

severe, episodes. The dietary history reveals a monotonous intake of the pattern already described.

Upon physical examination, the pellagrin may be somewhat underweight, with varying degrees of dehydration, depending upon the severity of the gastrointestinal disturbance. The characteristic skin lesions (Figs. 93, 94) are the symmetric



FIG. 93. Photograph of a pellagrin, on admission, showing marked dermatitis over face and neck, and extensive and severe glossitis with membranes on the margins of the tongue. There were plugs in the orifices of the sebaceous glands and fissures at the corners of the mouth. (Courtesy, Smith and Ruffin: *Internat. Clinics*, 2:103, 1940.)

changes of the exposed surfaces, especially over the wrists and tops of the feet. In addition, one may find the so-called "dyssebacia" around the nose, mouth, and forehead—i.e., the plugging of sebaceous glands with dry, yellowish material. These lesions are often termed "shark skin." Over bony prominences, such as the knees and

elbows, hyperkeratotic areas associated with increased pigmentation are frequent. Such lesions occur most often in those pellagrins who have been bedridden for a period of time. Excoriations are common in the genital region, especially in the female. A bright red, sore tongue, sometimes described as beefy in appearance, is usual. Finally, cheilosis and angular oral fissures may be encountered. In many instances, the cheilosis and angular fissures respond to niacin therapy; but in others, they do not heal until riboflavin is administered. Dyssebacia may follow similar therapeutic patterns.

**Laboratory Findings.** No decisive chemical tests exist for the detection of pellagra. The occurrence of abnormal urinary pigments has been reported in this disease, but much confusion exists concerning the identity and significance of these substances. The niacin metabolite, N<sup>1</sup>-methylnicotinamide, may be rendered fluorescent and, hence, conveniently measured. The urinary excretion of this material is decreased in the presence of both mild and severe clinically manifest nicotinic acid deficiency. This decrease is apparent in either 24-hour urinary specimens or in timed specimens following a standardized test dose of nicotinamide. Because of the very great overlapping of values between deficient patients and those showing no evidence of niacin deficiency, this test is of little value in establishing the diagnosis in an individual case. Blood and tissue coenzyme concentrations have not proved of clinical value to date.

As previously indicated, the pellagrin may or may not exhibit an anemia, which varies from microcytic to macrocytic in character. Laboratory findings related to the hematologic picture obviously depend upon the etiology of the anemia.

**Diagnosis.** The diagnosis of pellagra rests upon the clinical and dietary history, the clinical findings, and response to specific therapy. Evaluation of the latter point is rendered difficult unless the patient is carefully controlled in order to prevent the occurrence of spontaneous remissions due to bed rest and improved dietary intake.

The distinction between sprue and pellagra is sometimes a problem, but can usually be made upon consideration of the following points: (1) A more severe macrocytic anemia is the rule in sprue. (2) Pellagrous dermatitis is not seen in



FIG. 94. Photograph of the hands of the same patient on admission. Similar but less extensive lesions were present on the feet. (Courtesy, Smith and Ruffin: *Internat. Clinics*, 2:103, 1940.)

sprue, unless the two diseases coexist. (3) Although diarrhea is present in both diseases, steatorrhea and its concomitant findings are not usually encountered in pellagra. (4) The oral glucose tolerance test is not significantly abnormal in pellagra. (5) The response to specific therapy differs.

Mild clinically manifest nicotinic deficiency may be characterized entirely by vague symptoms of early pellagra and glossitis and, in some cases, angular fissures. In such instances, the condition must be differentiated from arthroflavinosis, chronic iron deficiency, pernicious anemia, pseudoarthroflavinosis, allergic glossitis, and even lingual neoplasms. If mental symptoms predominate, the disease may be confused with psychoses of various origins.

**Treatment.** The predominant symptoms of pellagra are relieved by administration of niacin in doses of 50 mg. two or three times a day orally. If the patient's condition contraindicates oral administration, nicotinamide (100 mg. daily) may be given parenterally. Such specific therapy should be accompanied by an adequate diet of relatively high-protein, high-vitamin content.

Additional dietary supplements may be given

as indicated by the presence of evidence of specific deficiencies. Crude oral liver extracts have proved of particular benefit in the restoration of many pellagrins.

General supportive measures should be instituted as in any disease. In the presence of dehydration, prompt administration of saline and glucose is necessary. Bed rest, good nursing care, and sympathetic encouragement to consume a liberal diet should be part of the treatment of all such patients.

Continuous maintenance therapy with niacin is unnecessary after subsidence of the disease. It is essential, however, that the patient's eating habits be altered in order to allow for the consumption of a truly adequate diet.

**Prognosis.** The prognosis in pellagra depends upon the severity of the disease. In the usual mild or moderately severe cases, mortality should approach zero, unless the disease be complicated by some more serious disturbance. In severely ill groups, death may occur despite the most skillful handling. For example, at Duke University the mortality of 3.7 per cent is reported for the group of patients who were treated shortly after the introduction of nicotinic acid.

Vigorous early therapy of patients with mental changes results in recovery. If the dementia has been of long standing, however, permanent residua may result.

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### Ariboflavinosis

William J. Darby

Definition  
Etiology  
Pathologic Findings  
Clinical Picture  
Laboratory Findings  
Diagnosis  
Treatment

**Definition.** Ariboflavinosis is the syndrome of angular oral fissures, corneal vascularization and photophobia, and lingual and skin changes which result from riboflavin (vitamin B<sub>2</sub>) deficiency.

**Etiology.** Ariboflavinosis is usually a dietary deficiency disease. It is frequently associated with evidences of deficiency of other members of the vitamin-B complex. The syndrome is not common in the United States at the present time, although it was described frequently during the latter 1930's as occurring in pellagrins following therapy with nicotinic acid. It now seems probable that these cases represented examples of vitamin-B complex deficiency syndrome, a part of which syndrome responded to administration of niacin, but other manifestations of which were due to riboflavin deficiency.

Ariboflavinosis has been reported from various areas in the United States, Newfoundland, China, India, Malaya, Africa, and England. It seems to be relatively common in those regions

of the world where milk does not constitute a major food item.

**Pathologic Findings.** Studies of the pathologic changes in ariboflavinosis in man have been limited to gross observation and biomicroscopic studies. The oral lesions develop as a pallor of the mucosa of the lip at the angles of the mouth followed by maceration and the appearance of transverse fissures within a few days. Upon healing, the site of these fissures is marked by barely visible pinkish scars. The active lesions may become covered with a honey-colored crust; redness and swelling of the mucosa of the lip may develop at the height of the process. The lingual papillae may become lower, and the filiform papillae assume a mushroom appearance. The typical glossitis of riboflavin deficiency is described as magenta colored.

The skin around the angles of the nose and over the butterfly area of the face is often covered with fine, scaly, slightly greasy desquamation.

The corneal involvement in ariboflavinosis is first manifest as circumcorneal injection which may be evident grossly. The limbic vessels give rise to subepithelial capillaries which invade the cornea and are best seen with the slit lamp.

Keratitis with superficial opacities may occur. Numerous descriptions have been made of the microscopic changes in riboflavin deficiency in experimental animals.

**Clinical Picture.** The clinical picture of ariboflavinosis varies, depending upon the predominant lesion. When ocular manifestations are prominent, the patient complains of photophobia and dimness of vision, a burning sensation of the eyes, roughness or a "sandpaper" feeling of the eyelids, and blurring of vision. Photophobia may be pronounced. The conjunctivas are injected, a change especially noted in the periorbital region. Corneal vascularity is observed with either the slit lamp or the ophthalmoscope. Opacities of the cornea may be present.

Angular fissures, cheilosis, and glossitis may be present. These findings are frequently associated with the dermatitis described above. Oral or ocular lesions may be present alone or in combination. Manifestations of ariboflavinosis may be the sole deficiency sign detectable, or changes characteristic of pellagra may be associated.

Careful inquiry into the dietary history of the patient reveals a diet devoid of those foods rich in riboflavin—milk, liver, lean meat, green leafy vegetables, and the like.

**Laboratory Findings.** There exist no characteristic laboratory findings in ariboflavinosis. Riboflavin excretion in the urine is decreased whether measured on a 24-hour specimen or following a load test. It is not possible at this time, however, to state that a given urinary excretion level will necessarily be associated with clinically manifest disease. A high urinary excretion value makes unlikely the diagnosis of ariboflavinosis.

**Diagnosis.** The clinical picture, the dietary history, and an associated low urinary excretion of riboflavin should lead to the consideration of ariboflavinosis as a possible diagnosis. The rapid specific response to riboflavin aids in the establishment of the diagnosis.

The ocular lesions of riboflavin deficiency are to be differentiated from conjunctivitis of various origins, and from keratitis due to injury, syphilis, and other causes. Examination of the cornea of healthy individuals with the slit lamp reveals that an occasional subject will show an asymptomatic vascular "streamer" or so in the cornea. Such findings are not to be confused with ariboflavinosis. In experimental animals, deficiencies of a relatively large number of other vitamins

and amino acids may result in corneal vascularization. Obviously, then, the presence of this sign alone cannot be taken as a specific indicator of riboflavin deficiency.

The angular fissures and glossitis of riboflavin deficiency must be distinguished from those lesions due to deficiency of nicotinic acid. A careful dietary history may be of value in making this distinction. The patient with niacin deficiency usually gives a history of considerable intake of corn, while ariboflavinosis has not been so closely related to an intake of maize. Milk is rich in riboflavin but very low in niacin. History of an intake of a pint of milk per day almost eliminates riboflavin deficiency. On the other hand, the key to differential diagnosis may lie in response to specific therapy. As noted above, the two deficiencies may coexist. Glossitis and angular fissures are not infrequently encountered in iron deficiency. The findings of a hypochromic microcytic anemia is of value in differentiating these two deficiency manifestations. Angular fissures resistant to riboflavin therapy are often noted in older patients with ill-fitting dentures. These lesions, presumably due to the distortion of the labial angles, have been termed "pseudo-ariboflavinosis." Some cases of angular fissures have been reported as responding to treatment with other members of the B complex, particularly pyridoxine and pantothenic acid.

**Treatment.** The prevention of ariboflavinosis resides in the ingestion of 1 mg. or more of riboflavin in the diet daily. The daily recommended allowance (Table 46) is at a somewhat higher level. This quantity may easily be obtained by including daily portions of milk, lean meat, green leafy vegetables, and occasional servings of organ meats in the diet.

Specific curative therapy consists of the oral administration of 5 to 15 mg. of riboflavin daily. In addition, an effort should be directed toward correction of the dietary pattern of the patient with the regular inclusion of good sources of this vitamin in the diet.

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### Thiamine Deficiency (Beriberi)

William J. Darby

Definition
Etiology
Pathologic Findings
Clinical Picture
Laboratory Findings
Diagnosis
Treatment
Prognosis

**Definition.** Beriberi is a deficiency disease characterized by multiple neuritis, changes in the cardiovascular system, and frequently edema. The primary manifestations are attributable to thiamine lack.

**Etiology.** Thiamine is a water-soluble, heat-labile vitamin, the principal food sources of which are whole cereals, legumes, lean meats (especially organ meats), nuts, and yeast. Highly refined foodstuffs, such as milled rice, low-extraction flour, and refined sugar, are practically devoid of the vitamin. The dietary requirement of thiamine is related directly to the intake of non-fat calories. Fat and, to a lesser extent, protein exert so-called "thiamine-sparing action."

The typical diet associated with the development of beriberi is a monotonous low-protein, low-fat, high-carbohydrate diet in which a highly milled cereal such as rice is the chief source of calories. The existence of this food pattern accounts for the distribution of beriberi in the Orient, in many of the islands of the Pacific, in sections of the West Indies, South America, and Africa, and in circumscribed regions of North America (the rice-growing area of southern Louisiana and, formerly, Newfoundland).

The sporadic case of beriberi in the United States is commonly associated with alcoholism.

In contrast to the earlier belief that this association was due to an increased use of thiamine in the metabolism of alcohol, it is due to the displacement of thiamine-containing foodstuffs by alcohol. Alcohol, surprisingly enough, has a thiamine-sparing action.

Beriberi is seen in both sexes and at all ages. In the United States the majority of reports indicate a predominance in men. In the Orient and the Philippines, however, the disease not infrequently complicates pregnancy or lactation. It may occur in the breast-fed infant or, in rare cases, as a congenital disease of the newborn.

There is no doubt that beriberi is a deficiency disease. In addition, there are opinions that its development is at times attributable to consumption of dirty or spoiled rice which, presumably, contains a hypothetic beriberi-producing factor. Thiaminase, an enzyme occurring in certain fish, destroys the vitamin and, hence, may render a food deficient in thiamine. Synthetic antimetabolites for thiamine have been produced; none, however, has been isolated from foodstuffs. Live yeast, when introduced into the gastrointestinal tract, "soaks up" thiamine, converts it to a phosphate derivative, and renders it unabsorbable. Whether there are other organisms with similar activities has not been ascertained. The role of these several influences in the induction of thiamine deficiency in man has not been defined.

**Pathologic Findings.** The pathologic findings in beriberi are marked by their nonspecificity and lack of constancy. The most important lesions

are noted in the heart and peripheral nerves. The heart may be enlarged, particularly to the right. This enlargement is usually due to cardiac dilatation, although hypertrophy has been described. Microscopically there may be seen degenerative changes in the cardiac muscle, interstitial edema, and hydropic degeneration of the myocardial fibers.

Degenerative changes involving the central, peripheral, and autonomic nervous systems may exist. Degeneration of the myelin sheath and fragmentation of the axis cylinder comprise the most frequently described lesion of the peripheral nerve. Swelling and chromatolysis of the sympathetic chain and degeneration of the vagus nerve are found in some cases.

It is not possible to ascribe specifically to thiamine deficiency these pathologic changes which occur in beriberi. Some of the findings may be due to concomitant deficiencies of one or another dietary factor other than thiamine.

**Clinical Picture.** The clinical picture of beriberi may for convenience be divided into three types: (1) wet beriberi, in which there predominates the finding of edema and serous effusions; (2) dry beriberi, in which the predominant picture is referable to the nervous system and edema is minimal or absent; and (3) acute cardiac beriberi, in which the cardiac symptoms predominate and in which sudden death may occur.

At least three months on a grossly deficient diet are required for the development of beriberi. The onset is seldom acute but rather is marked by gradually increasing fatigability, irritability, cardiac palpitation, muscle tenderness (especially of the calf muscles), and leg pains exacerbated by assuming a squatting position; the appearance of paresthesias, superficial hyperesthesia, loss of superficial cutaneous sensation, and diminution of deep reflexes mark the development of the peripheral neuritis. Flaccid paresis, foot drop, and muscular wasting may follow. The peripheral neuritis first appears in the lower extremities and may later develop in the upper extremity.

During the initial phases of the peripheral neuritis, edema may appear in the so-called "wet type" of beriberi. The edema is first noted around the ankles and, initially, it disappears after a few hours in bed. It may progress, however, to generalized anasarca with pleural, peri-

toneal, and pericardial effusions. In the absence of cardiac failure, the cause of this edema is unknown.

Clinicians working in China have described two types of cardiac beriberi: (1) the acute fulminating disease which appears suddenly and, if untreated, results in death within a few hours; and (2) the less acute case with beriberi heart disease and congestive failure. The patient with beriberi heart complains of excessive fatigue, palpitation on exertion, and shortness of breath. In the congestive type, edema is always present, the pulse rate may or may not be increased, and the cardiac rhythm and blood pressure may be normal or elevated. The circulation time is decreased, venous pressure may be elevated or normal, and less difference than normal exists between the oxygen content of arterial and venous blood. Electrocardiographic changes are variable and nonspecific. Finally, dramatic recovery follows specific therapy with thiamine. The recovery is marked by relief of general symptoms, diuresis, and a progressive decrease in cardiac size over a period of a few weeks.

Some clinicians feel that less rigid criteria for the diagnosis of beriberi heart disease should be accepted, and the following have been proposed: (1) insufficient evidence for other etiology, (2) three or more months on a thiamine-deficient diet, (3) signs of neuritis or pellagra, (4) enlarged heart with sinus rhythm, (5) dependent edema, (6) elevated venous pressure, (7) minor electrocardiographic changes, and (8) recovery with decrease in heart size or autopsy consistent with beriberi heart disease.

Other deficiency diseases, such as avitaminosis A, pellagra, or anemia, may be associated with the beriberi syndrome.

**Laboratory Findings.** Many laboratory procedures have been used for the investigation of thiamine metabolism in man. Among these may be mentioned the determination of thiamine in the blood, of thiamine level of the white cell platelet layer, and of the 24-hour urinary excretion of thiamine, and various load tests in which the urinary excretion of thiamine is determined following standardized doses of the vitamin. Unfortunately, none of these is dependable clinically for the establishment of the diagnosis of beriberi.

Probably the most promising test for the diagnosis of thiamine deficiency state is the determination of the carbohydrate metabolism index

(CMI). In the absence of thiamine, the metabolism of pyruvic acid is impaired inasmuch as a thiamino-protein enzyme has to do with the de-carboxylation of pyruvic acid. Slightly elevated basal pyruvic acid concentrations (above 1.2 mg. per 100 ml.) occur in severe beriberi. Except in severe thiamine deficiency, the determination of fasting pyruvic acid levels in the blood is not a reliable indicator of thiamine deficiency. The rate of disposal (and, hence, the blood concentration) of pyruvic acid depends partly upon the metabolic load of glucose and lactic acid. Accordingly, the simultaneous determination of these three constituents under proper conditions seems to provide one with more useful information concerning thiamine status. The procedure is as follows: Nine ml. of 20 per cent glucose per kilogram is administered orally after withdrawing a fasting basal blood sample. Sixty minutes later a mild exercise test is applied. This consists of walking down and up and down and up and down again a flight of 21 steps 19 cm. high in a period of 60 seconds. Five minutes later, blood is again sampled. The CMI, as was empirically developed, is calculated by the formula:

$$\text{CMI} = \frac{L - \frac{G}{10} + 15P - \frac{G}{10}}{2}$$

G, L, and P, respectively, are levels of glucose, lactic acid, and pyruvic acid in milligrams per 100 ml. of blood. Based on studies of induced thiamine deficiency in man, 15 has been set as the upper limit of normal CMI. Although this test has not been applied to patients with frank beriberi, there is reason to believe that it should prove a useful diagnostic tool.

**Diagnosis.** The diagnosis of beriberi is made from the history, physical findings, and controlled response to specific therapy. Pyruvic acid levels, or CMI, may be useful diagnostic procedures. The measurement of cardiac size by x-ray is especially valuable as a means of evaluating the effect of specific therapy. Two tests of especial value in examining for peripheral neuritis of beriberi are: (1) Have the patient squat on his heels and determine whether this produces leg pain and whether he is able to rise without using his hands. (2) Squeeze the calf muscles to test for tenderness.

Peripheral neuritis, when present, must be dif-

ferentiated from the neuritis of lead poisoning or arsenic. The history, the absence of edema in toxic neuritis, the presence of a lead line on the gums, or the presence of stippled cells in the blood smear serves to distinguish these.

**Treatment.** Preventive therapy consists in the establishment of proper dietary habits which will ensure sufficient intake of the vitamin (see Chapter 40, table 46). Curative treatment consists of the administration of thiamine orally or parenterally. When given orally, doses of 3 to 5 mg. may be given two or three times a day. The evidence indicates that oral doses larger than 5 mg. are no more efficient, due to limitation of absorption. Five to 25 mg. of thiamine hydrochloride parenterally per day may be given. The oral route is to be preferred except in critical cases, and, once response has begun in these, oral administration may safely be substituted. Along with the specific therapy, every effort should be made to correct faulty dietary habits responsible for development of the deficiency. Provision of a liberally adequate diet is of added value in many cases because of the accompanying deficiencies.

**Prognosis.** The prognosis in beriberi depends upon the stage of the disease and the time which elapses before proper therapy is instituted. Properly instituted therapy results in a remarkably rapid remission in most uncomplicated cases. On the other hand, a death rate as high as 50 per cent has been reported for "occidental beriberi heart disease" in recent years. This has been attributed to the establishment of an irreversible process.

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# Avitaminosis A and Hypervitaminosis A

William J. Darby

## Avitaminosis A

- Definition
- Etiology
- Occurrence and Epidemiology
- Physiology of Vitamin A
- Pathologic Findings
- Clinical Picture
- Laboratory Findings
- Diagnosis
- Treatment
- Prognosis

## Hypervitaminosis A

### AVITAMINOSIS A

**Definition.** Vitamin A deficiency results in a syndrome called avitaminosis A. The syndrome may be manifested by an impaired capacity for dark adaptation, night blindness (nyctalopia), xerophthalmia, the occurrence of Bitot spots, and hyperkeratotic lesions of the extensor surfaces of the skin.

**Etiology.** Avitaminosis A may be due to a dietary lack of vitamin A or its precursors (carotenes) or to failure to absorb these lipid-soluble substances due to alterations in absorption of fat. Conditioned deficiencies are likely to be found in sprue, celiac disease, fibrocystic disease of the pancreas, intestinal lipodystrophy, and other states associated with steatorrhea. The long-continued ingestion of mineral oil with meals may render unabsorbable carotene or vitamin A, and thereby lower significantly the nutrition of the individual, particularly where the dietary contains borderline amounts of vitamin activity largely derived from carotene. In hepatitis and cirrhosis of the liver, decreased blood levels of vitamin A may be encountered. It may be that the impairment of dark adaptation noted in hepatic cirrhosis is, in part, evidence of a defect in the metabolism of vitamin A.

**Occurrence and Epidemiology.** Avitaminosis A is uncommon in the United States. Dietary deficiencies of vitamin A have been reported frequently from the Orient, India, southeast Asia, Africa, and, formerly, northern Europe. The reports from northern Europe were chiefly of institutionalized children. Rare cases of severe avitaminosis A have been reported from the

United States. In most instances, however, these have been conditioned deficiencies.

This deficiency disease is more likely to be encountered in infants than adults for two reasons: (1) The requirement of the vitamin is higher for growth than for simple maintenance. (2) The newborn has relatively small stores of the vitamin and, hence, is more easily depleted by a deficient diet.

**Physiology of Vitamin A.** Vitamin A is a fat-soluble, high-molecular-weight alcohol of unsaturated structure and, hence, easily destroyed by oxidation. Its absorption is dependent upon normal absorption of fats, and it appears in the lymphatics following ingestion. Water-dispersible or emulsified preparations of vitamin A are better absorbed in those conditions in which fat absorption is impaired.

Vitamin A is stored in the liver of the well-fed adult in quantities sufficient to meet estimated requirements for a period of 200 to 400 days or longer. Only negligible quantities are normally excreted in the urine, although there is increased excretion in some renal diseases and infections.

Carotenes serve as precursors of vitamin A, the site of conversion being either the liver or the intestinal wall. Carotene is less efficiently absorbed than vitamin A; and if the total vitamin A requirement be met from carotene alone, the minimal requirement is greater than if the dietary source is preformed vitamin A.

It is well established that vitamin A enters into the constitution of visual purple (rhodopsin). When light falls on the retina, visual purple is broken down. Accordingly, there is a constant cycle of breakdown and resynthesis of this derivative of vitamin A. In the absence of vitamin A, the resynthesis is retarded and nyctalopia occurs.

**Pathologic Findings.** Vitamin A is concerned with the maintenance of normal integrity of certain epithelial tissues and the orderly development of bones and teeth. Widespread epithelial lesions are characterized by atrophy, and pro-

liferation of the basal cells with metaplasia into stratified keratinizing epithelium. It is sometimes difficult to separate the epithelial changes seen at autopsy into those due to avitaminosis A and those attributable to associated conditions, such as fibrocystic disease. Corneal lesions may be especially noteworthy, with keratinization of the epithelium followed by infiltration and vascularization and sometimes ulceration. Alterations in the lacrimal glands may result in atrophy and fibrosis, and these processes may account for the ocular xerosis. No general agreement can be obtained on this point, however. Skin lesions attributed to vitamin A deficiency are follicular, somewhat pigmented papules with a central core consisting of a keratinized epithelial plug. Histologic study shows hyperkeratinization and hyperplasia of the epithelium with associated degeneration of the sweat glands. To these changes is attributed the dryness of the skin. The specificity of these lesions has recently been questioned, and some workers hold that the skin lesions are due to associated B-complex deficiencies.

Important pathologic changes occur in the skeleton, nervous system, teeth, retina, and other structures in experimental deficiencies in lower animals. These have not been clearly identified in man.

**Clinical Picture.** The clinical picture of avitaminosis A varies with the age of the subject; in infants, xerophthalmia and night blindness are the most frequent manifestations. The nutritional history of the infant indicates a diet lacking in vitamin A or carotene, or else an associated disease, such as cystic fibrosis of the pancreas or biliary obstruction, which would lead to defective absorption of vitamin A. In the adult, xerophthalmia occurs but rarely, and then in the more advanced cases. The earliest clinical manifestation of vitamin A depletion in the adult is decreased dark adaptation detectable by one of the several adaptometers. Some time later, clinical night blindness develops.

Skin changes consist of generalized dryness of the skin or xeroderma followed by the appearance of localized papular eruptions on the anterolateral aspect of the thighs and posterolateral surfaces of the upper arms. These lesions may involve extensor surfaces of both upper and lower extremities and then extend over the buttocks, shoulders, abdomen, and neck. The distribution is symmetric and the skin over the

involved sites generally appears darker than normal. On close examination, the lesions are seen to be horny plugs projecting from the hair follicles. These findings are described with increasing frequency after puberty, but are rare before that age. Prior to the onset of puberty, skin changes of avitaminosis A are primarily those of dryness without the associated hyperkeratosis. Failure to recognize this point has led to much confusion. The common childhood lesion of keratosis pilaris has often been mistakenly attributed to avitaminosis A, despite the fact that it is not associated with any of the other findings of A deficiency, is associated with satisfactory blood levels of vitamin A, and does not respond to administration of the vitamin.

Bitot spots are characteristic grayish white, foamlike, superficial lesions of the conjunctiva. The lesion is usually seen in both eyes and occurs most frequently on the lateral aspect of the bulbar conjunctiva. These changes are widely held to be manifestations of avitaminosis A. They often disappear upon the administration of the vitamin, but this is by no means a constant finding. Bitot spots are easily differentiated from the thickened, gelatinous-appearing, triangular pingueculae which are encountered very commonly in adults and which are not manifestations of vitamin A deficiency.

**Laboratory Findings.** Under conditions of vitamin A and carotene restriction there occurs a moderately rapid fall of carotene in the serum of the adult. Within three months after the start of a vitamin A- and carotene-free diet, the plasma levels fall to a stable concentration of from 10 to 40 I.U. per 100 ml. (6 to 24  $\mu$ g. per 100 ml.). Total carotene content of plasma of well-nourished individuals usually ranges upward from 120 to 300 I.U. per 100 ml. (72 to 180  $\mu$ g. per 100 ml.). In states of deprivation, the very low carotene values may not actually represent biologically active precursors of vitamin A but, instead, other carotenoid pigments. Concentrations of carotene less than 80 I.U., or 50  $\mu$ g., per 100 ml. are presumptive evidence of low dietary intake or some impairment of absorption.

Under conditions leading to a deficiency of vitamin A, the blood concentration of the vitamin itself falls much more slowly than does the concentration of carotene. No appreciable fall in vitamin A concentration occurs in adults until after about eight months on a diet totally devoid

of the vitamin or its precursor. It is widely accepted that values of vitamin A as low as 70 I.U. per 100 ml. are consistent with health. Concentrations as low as 50 I.U. per 100 ml. are not infrequently encountered in otherwise healthy individuals. Deterioration of dark adaptation does not appear to occur until the plasma level has fallen below 50 I.U. per 100 ml. Concentrations below 40 or 50 I.U. per 100 ml. may at times be associated with defective night vision or other clinical manifestations of avitaminosis A. On the other hand, they may be encountered in apparently healthy adults. Clinical findings due to vitamin A deficiency are consistently accompanied by plasma levels below 40 or 50 I.U.

Blood levels of vitamin A are normally lower in infants, the newborn, and in the later part of pregnancy. Infant's blood is usually low or devoid of carotene.

**Diagnosis.** The diagnosis of avitaminosis A may be made upon finding the suitable combination of signs, a history of the diet low in vitamin A or carotene over a long period of time or of some defect in absorption which might effectively decrease the absorption of vitamin A and carotene, coupled with consistently low blood levels. The detection of a definitely abnormal final rod threshold and of lengthening of the cone-rod transition time in measurement of dark adaptation is of value in establishing the diagnosis of avitaminosis A. The subsequent response of these abnormalities of adaptation to administered vitamin A or carotene is further evidence in support of such diagnosis. As with all the vitamin deficiency diseases, the response to a therapeutic test is of additional value in establishing the correct diagnosis.

**Treatment.** The treatment of avitaminosis A should be divided into preventive and curative forms. Preventive therapy consists of the establishment of proper dietary habits in order to ensure a sufficient intake of the vitamin (see Chapter 40, table 46).

Curative treatment consists of administration of 5000 to 25,000 I.U. of vitamin A or an equivalent amount of carotene daily for a period of some six weeks or until the lesions have cleared. If the avitaminosis is conditioned by faulty absorption, it may be that one of the water-dispersible preparations of vitamin A would be more effective. Following this, complete therapy involves correction of the dietary defect and/or

conditioning abnormality underlying the development of the disease syndrome.

**Prognosis.** The prognosis in cases of avitaminosis A is good except where corneal involvement is sufficiently extensive to result in permanent scarring. In these instances, permanent blindness may result despite the clearing of the xerophthalmia.

### HYPERVITAMINOSIS A

Hypervitaminosis A results from a greatly excessive intake of vitamin A, usually in the form of concentrates or high-potency fish liver oils. Because of the large margin of safety between active therapeutic dose and toxic quantities of the vitamin, the condition is relatively rare. Nevertheless, on occasions the ingestion of amounts of vitamin A from about 250,000 I.U. upward per day over a sufficient period of time has resulted in a picture of toxicity.

The syndrome of hypervitaminosis A is characterized by hepatomegaly, splenomegaly, leukopenia, anemia, periosteal changes, sparse, coarse hair, increased serum vitamin A levels, and increased serum lipids. The serum vitamin A values may range from 600 to 1000 I.U. per 100 ml. An increased bleeding tendency, probably due to hypoprothrombinemia, may be observed.

The toxicity of polar bear and seal liver has been attributed to the tremendously high vitamin A content of these tissues. It is held that the acute symptoms of drowsiness, irritability, severe headache and vomiting, and "peeling of the skin" which may occur after ingestion of polar bear liver may be explained on this basis.

Upon withholding of vitamin A, the hypervitaminosis subsides gradually over a two- or three-month period. Specific therapy is unnecessary unless hypoprothrombinemia occurs, in which event administration of vitamin K may be of use.

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# 48

## Avitaminosis D (Rickets) and Hypervitaminosis D

William J. Darby

- Avitaminosis D
- Definition
- Occurrence
- Etiology
- Pathology
- Clinical Picture
- Laboratory Findings
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- Prevention and Treatment
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### AVITAMINOSIS D

**Definition.** The discussion of rickets is here restricted to the nutritional disease which is characterized by impaired absorption of calcium with alterations in calcium-phosphorus metabolism which result in impaired mineralization of bone with consequent abnormalities of structure and shape of the bones. The primary deficiency is that of vitamin D. More broadly, however, rickets is to be considered as osteomalacia in children, and may result from an inadequate intake of calcium from any cause or an excessive loss. For a detailed treatment of the broad etiologic concept of osteomalacia the reader is referred to Chapter 68 (Osteomalacia and Rickets).

**Occurrence.** Rickets due to vitamin D deficiency is primarily a disease of the temperate zone and of large towns and thickly populated

industrial regions. It is not possible to give a precise, quantitative estimate of the incidence of rickets in the general population. Any such estimate would vary, depending upon the diagnostic criteria adopted. There is no doubt that the disease is of much less frequent occurrence today than it was two or three decades ago. That it still exists, however, is emphasized by a study of the autopsy findings of children who died in the Johns Hopkins Hospital during the 14-year period ending in 1942. The pathologic examinations revealed an incidence of 48 per cent with some degree of rachitic change.

**Etiology.** Rickets is due primarily to the lack of vitamin D. Vitamin D may be ingested in foods or formed within the skin by the ultraviolet irradiation of 7-dehydrocholesterol. The irradiation of this sterol produces the vitamin. For avitaminosis D to develop, therefore, it is necessary that the diet be deficient in the preformed vitamin and that the subject not be exposed to ultraviolet light of the wave length which will convert 7-dehydrocholesterol into the active vitamin.

Only ultraviolet light of the wave length within the range of approximately 250 to 310 milli-

microns is active in the conversion of precursors of vitamin D to vitamin D (hence, possesses antirachitic potency). The wave lengths of solar radiation range upward from approximately 290 millimicrons. Accordingly, sunlight possesses antirachitic properties, and where the solar radiation is intense and is not obstructed by fog, clouds, smoke, or other atmospheric conditions, it provides some protection against rickets. For this property of sunlight to be effective the shorter ultraviolet rays must contact an appreciable portion of the skin surfaces. Heavy clothing or ordinary window glass will obstruct active ultraviolet irradiation from the sun. Furthermore, it is commonly stated that the pigmented skin of the darker races serves to "filter out" the antirachitic rays and that the greater frequency of rickets in the Negro in the United States may be attributed to this phenomenon. Economic and dietary factors are most likely of considerable importance also in this differential.

Rickets is observed most frequently during the ages of most rapid growth—that is, between 6 and 18 months. The disease does not occur unless the child is growing. Rickets is seen less frequently in the breast-fed infant than in the artificially fed one, chiefly because of the more favorable calcium-phosphorus ratio of breast milk. While the rachitogenic effect of phytate or phytic acid may become important in a child population fed a high-cereal, low-milk diet, this is not the primary factor in the disease as usually encountered in the United States.

Cases have been reported of individuals who appear to have a "raised resistance to vitamin D (RRD)." These subjects present the clinical picture of rickets on ordinary intakes of vitamin D, but this disease may be controlled by administration of very large quantities of vitamin D-containing preparations. This is discussed along with the so-called rickets due to altered renal function and osteomalacia in Chapter 68.

**Pathology.** The lesions of rickets are primarily those of disturbances of growth and calcification of bone. Normally, the long bones increase in length by a process of continuous proliferation and maturation of the cartilage cells of the epiphysis. During maturation, the older cartilage cells align themselves in parallel rows at the junction of ossification, and calcium salts are deposited in the cartilaginous matrix lying between these rows of cells. The oldest cells nearest the area of bone

formation disintegrate, and the lacunas are invaded by proliferating blood vessels which, in turn, are accompanied by osteoblasts. These cells deposit osteoid, the organic matrix of the new-forming bone, and in this osteoid is laid down the inorganic salts of calcium and phosphorus to give rise to the new bone. During the process of continuing growth, any given portion of this new bone may be resorbed as the whole structure undergoes remodeling and molding.

In rickets there appears to be interruption of this normal process at the stage of deposition of calcium and phosphorus salts in the deposited osteoid. Osteoblastic activity proceeds with the laying down of osteoid, but this is not ossified in the normal fashion. In addition, there is failure of destruction of the older cartilage cells, of vascularization of the areas which would normally be invaded by proliferating blood vessels, and of calcification of the cartilaginous matrix.

In contrast to the normal costochondral junction with its narrow, sharp, well-demarcated union between cartilage and bone, the rachitic junction presents a broad, disorganized band with a wide zone of proliferative cartilage cells and considerable irregularities in the calcification. Grossly, the costochondral junction appears as an enlarged, softened, irregular process which is recognized clinically as beading of the ribs or enlarged wrists, and the like.

**Clinical Picture.** The clinical picture of rickets may vary from the very mild, barely detectable disorder to the full-blown disease. In the mildest cases the child is somewhat irritable, and restless during sleep, and may present almost no physical signs other than slightly exaggerated beading of the ribs. The severe disease may be manifest by widespread bony deformities in a fretful, pale, ill child.

The bony deformities are the most characteristic findings. Enlarged costochondral junctions (rachitic rosary), while not pathognomonic of rickets, is one of the earliest of detectable signs. The most severe beading which accompanies long-continued rickets may be associated with flaring of the lower ribs and a depression along the line of attachment of the diaphragm (Harrison's groove). Retraction of the sternum to form the so-called "funnel chest" may or may not be present.

In the moderate or more severe cases of rickets, the head appears large with prominent frontal

bosses, there may be flattening of the crown, and areas of softening of the cranial bones may be detected upon palpation. The presence of these softened areas is termed "craniotabes." Delayed closure of the sutures may be noted.

In cases of some duration, the long bones exhibit enlargement of the metaphyses, especially noticeable at the wrists, knees, and ankles. Varying degrees of bony deformities, such as bowing of the legs, knock-knees, and pelvic deformities, may be apparent, depending upon the duration of the process and the amount of stress to which the skeleton has been subjected.

The musculature generally is lax, and this, in association with the rachitic bone changes, gives rise to protuberant abdomen aptly termed "pot belly."

Any one or a combination of the above signs may be present in varying degrees of severity. On the other hand, the signs may occur in the absence of a rachitic process. Accordingly, diagnosis cannot be made on the basis of the physical findings alone. Roentgenologic examination of moderate to advanced cases of rickets reveals cupping of the ends of the bones, especially of the ulna, a frayed margin at the epiphyseal end of the shaft, and diminished calcification of the shafts. X-ray examination is less helpful in efforts to establish the diagnosis of mild rickets, as many of the normal changes in growing bone may easily be confused with slight alterations sometimes attributed to rachitic processes.

Hypocalcemic tetany may occur in severe rickets.

**Laboratory Findings.** The laboratory findings encountered in rickets and their physiologic relationships are discussed in Chapter 68.

**Diagnosis.** The diagnosis of rickets is suggested by the history and the presence of combinations of the symptoms and signs already discussed. In conjunction with roentgenologic changes and laboratory evidence of increased serum phosphatase, normal to low serum calcium and/or inorganic phosphorus, and a history of circumstances which would lead to deprivation of vitamin D enable one to make a diagnosis of rickets. The rachitic rosary may be confused with costochondral beading of scurvy, but the presence of bone tenderness in scurvy should make the differentiation from rickets. Other conditions, including chronic nephritis, the Fanconi Syndrome, and hypoparathyroidism likely to be

confused with rickets due to avitaminosis D are discussed in Chapter 68.

**Prevention and Treatment.** Although exposure to ultraviolet light (sunlight or artificial light) can prevent rickets, the most practical preventive measure is the administration of a dependable source of vitamin D. Administration of vitamin D in quantities to provide from 400 to 800 International Units of D activity per day serves as a dependable preventive measure. The method of administration is not critical. Milk containing at least 400 I.U. of vitamin D per quart will suffice to prevent rickets in children. All of the milk fortified with vitamin D and accepted by the Council on Foods and Nutrition of the American Medical Association contains at least 400 I.U. of the vitamin per quart. Evaporated milks are fortified in amounts calculated to provide this quantity in the reconstructed fluid milk. It is important that children not receive overdoses of vitamin D in a too enthusiastic effort to provide abundant nutrition (see the section on Hypervitaminosis D below). Breast feeding of infants is advantageous in the prevention of the disease.

The treatment of active rickets consists in providing a well-planned diet which meets the nutritive requirements of the child, coupled with the administration of 4000 to 5000 I.U. of a dependable source of vitamin D per day. It is immaterial whether this be administered as cod liver oil, high-potency fish liver oil, fish liver oil concentrates, or viosterol. Larger quantities, if given, should be decreased when evidence of healing is well established. After healing has taken place, the usual preventive dose of vitamin D-containing preparation should be advised.

## HYPERVITAMINOSIS D

Hypervitaminosis D (see also Chapter 75) results from a greatly excessive intake of vitamin D. In sufficient dosage, it appears that any form of vitamin D will produce the picture of hypervitaminosis, regardless of the process by which the vitamin is made. In adults, vitamin D poisoning has been associated with the ingestion of approximately 100,000 I.U. or more of D preparations daily for a prolonged period of time. In infants, toxicity has been associated with the administration of 20,000 to 40,000 I.U. of vitamin D per day.

The syndrome of hypervitaminosis D is similar

in infants and adults. The most frequent symptoms are anorexia, nausea and vomiting, diarrhea (sometimes bloody in character), lassitude, muscular weakness, headache, drowsiness, and weight loss. Pruritis, polyuria, nocturia, dysuria, and psychic depression may also occur. Upon physical examination, one may find evidence of abnormal periarticular calcification. Brownish pigmentation of the skin has been reported. An exfoliative dermatitis may occur. The temperature may be subnormal or fever may be present in infants. Conjunctival injection and photophobia has been described in several instances. Impaired hearing and visual disturbances have occurred in a few patients. Moderate hypertension may or may not be present.

Laboratory examinations reveal an increased serum calcium level, essentially normal serum alkaline phosphatase values, and mild anemia. Serum phosphorus values may be high, normal, or low depending upon the intake. Renal damage is indicated by proteinuria, the presence of casts on microscopic study, an elevated nonprotein nitrogen, and impaired renal function as measured by the phenolsulfonphthalein and concentration tests. The characteristic x-ray finding is calcification of the periarticular structures. The bones themselves may show fairly definite osteoporosis. Metastatic calcification of other soft tissues occurs—for example, calcification of the prostate or kidney. In some of the fatal cases, extensive calcification of the inner portion of the media of arteries and of the heart valves has been described. Renal calcification has been reported in the lumen of collecting tubules, in the tubular cells, and in the arterioles.

The exact derangement in calcium metabolism in hypervitaminosis D remains to be determined. There occurs an increased absorption of calcium and an increased urinary excretion of the element. It is likely that the hypercalcemia is not the sole factor in the renal damage, inasmuch as proteinuria has been observed to occur under massive vitamin D dosage prior to the development of hypercalcemia.

Because of the widespread misuse of highly potent vitamin D preparations, hypervitaminosis D should be suspected in all cases of hypercalcemia. Careful questioning of the patient should reveal whether massive vitamin D ingestion has occurred. The absence of elevated serum alkaline phosphatase levels is useful in differ-

entiating the condition from the hypercalcemia of hyperparathyroidism. The hypercalcemias associated with multiple myeloma and skeletal neoplasms may be differentiated by roentgenologic pictures, history, and other blood chemical findings.

The outcome of the toxicity may be fatal unless administration of vitamin D is interdicted. Following cessation of administration of vitamin D, relatively prompt relief of the acute symptoms is usually obtained. Over a period of months the hypercalcemia disappears and the periarticular calcium deposits may be removed. Unless renal damage has become too severe, a gradual fall in nonprotein nitrogen may occur in association with other evidence of improved renal function, as the phenolsulfonphthalein test and renal concentration tests. Permanent renal damage may persist in some cases. Treatment consists of prevention by avoidance of massive dosing with vitamin D. Once the condition has occurred, however, interdiction of administration of vitamin D-containing preparations and establishment of a low calcium intake are the effective therapeutic steps.

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## Pancreatic Insufficiency

Kendall Emerson, Jr.

Fat  
Vitamins  
Nitrogen Metabolism  
Carbohydrate Metabolism  
Differential Diagnosis  
Treatment

Clinical symptoms of pancreatic insufficiency usually follow long-standing disease of the pancreas such as pancreatic lithiasis, recurrent acute pancreatitis, fibrosis, or tumors. Before metabolic disturbances become apparent there must be virtually complete absence of the external secretions of the pancreas in the duodenum. Pancreatic trypsin, lipase, and amylase are usually all equally involved, although one case has been reported in which only trypsin was absent.

As a result of the absence of these pancreatic enzymes in the intestinal tract, incomplete digestion and absorption of foodstuffs takes place, with secondary loss of accessory food factors. The metabolic disturbances which follow may be divided into four main groups, those associated with (1) fecal wastage of fat, (2) fecal wastage of vitamins, (3) fecal wastage of nitrogen, and (4) incomplete digestion and utilization of carbohydrate.

**Fat.** First to appear, and dominating the picture throughout, is the excessive loss of fat in the feces, known as steatorrhea. The stools become copious, unformed, soapy or foamy, and foul smelling. Total fecal fat may reach as high as 80 per cent of the dry weight of the stool and should be more than 40 per cent before steatorrhea can definitely be said to be present. The increase in fecal fat is primarily in the neutral fraction, but there is also a considerable increase in calcium and magnesium soaps.

Associated with this faulty absorption of fat there occurs weight loss and disappearance of the subcutaneous fat depots. At the same time there may be an increased amount of fat in the liver. This is due partly to the loss of pancreatic lipotropic factors which favor the removal of fat from the liver as phospholipid, and partly to excessive secretion of the pituitary ketogenic

hormone which is called forth to combat malnutrition by increasing the transportation of fat to the liver from the peripheral depots.

**Vitamins.** Even more important than the loss of fat, however, is the associated loss of the fat-soluble vitamins in the feces. The serum levels of carotene and vitamin A are low, and clinical signs of vitamin A deficiency may be present. The failure of absorption of vitamin D plays a much more important role than does calcium soap formation in the excessive loss of calcium in the feces and the resulting skeletal demineralization. This can be shown by the improvement in calcium absorption which follows ultraviolet irradiation of the skin whereby vitamin D is formed endogenously.

The possibility of vitamin E deficiency is suggested by the finding of deposits of a waxy, acid-fast staining material known as "ceroid" in the intestinal musculature, characteristic of this deficiency in animals as reported by Pappenheimer.

**Nitrogen Metabolism.** The incomplete digestion of protein associated with insufficient pancreatic trypsin in the intestinal tract results in an excessive loss of nitrogen in the feces after a meat meal. The presence of trypsin in the stools can be demonstrated in a very simple manner by merely placing a drop of a stool suspension on an unexposed x-ray film and incubating it for 30 minutes in the dark. If present, the trypsin will digest the gelatin surface of the film and cause an exposure. Trypsin is normally present in the stools of children but not of adults except in cases of diarrhea where there is rapid passage of the digestive juices through the intestinal tract. This test may, therefore, help to differentiate between pancreatic insufficiency and diarrhea from other causes in the adult, and is particularly useful in the diagnosis of pancreatic fibrosis in children.

The daily excretion of nitrogen may increase from the normal range of 1 to 1.5 Gm. to as much as 3 or 4 Gm. Generalized muscular wasting

ensues and hypoproteinemia and hypoaminoacidemia may occur; both albumin and globulin are equally reduced and there is no compensatory elevation of serum cholesterol, unlike most other conditions associated with hypoproteinemia. Generalized edema may occur, and edema of the intestinal tract further interferes with intestinal absorption.

**Carbohydrate Metabolism.** The disturbances in carbohydrate metabolism in pancreatic insufficiency are variable, depending upon the extent to which the islets of Langerhans have been destroyed and upon the degree of fatty infiltration of the liver. A flat glucose tolerance curve after oral glucose may be seen, but not so commonly as in idiopathic steatorrhea (see p. 50). More commonly there is some decrease in glucose tolerance which can be brought out or accentuated by relatively small doses of the pituitary adrenocorticotropic hormone (ACTH).

Flatulence, abdominal distention, and tympanites may result from faulty digestion of starch with resultant fermentation in the lower intestinal tract. These symptoms, however, are more frequently seen in generalized intestinal disorders such as sprue and celiac disease than in primary pancreatic insufficiency. Improvement in fat absorption following elimination of starch from the diet has been reported in celiac disease.

**Differential Diagnosis.** The metabolic disturbances occurring in idiopathic steatorrhea (sprue)

closely resemble those of true pancreatic insufficiency. The same excessive loss of fat, fat-soluble vitamins, nitrogen, and calcium occurs; and diarrhea, weight loss, muscular wasting, and skeletal demineralization ensue. Hypoproteinemia and edema are likewise common.

In idiopathic steatorrhea, unlike primary pancreatic disease, examination of the duodenal contents reveals the presence of pancreatic enzymes, and the increase in fecal fat is greater in the fatty acid than the neutral fat fractions. These patients, therefore, are usually not benefited by pancreatic extracts.

A macrocytic anemia of severe degree is a common finding in idiopathic steatorrhea, but unusual in pancreatic insufficiency. This anemia responds to folic acid, and less consistently to crude liver extract.

The oral glucose tolerance curve is always flat in idiopathic steatorrhea, whereas the intravenous curve usually is normal.

**Treatment.** Treatment is discussed in Chapter 263.

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# 50

## Sprue

William J. Darby

Definition  
 Classification  
 Etiology  
 Occurrence and Epidemiology  
 Pathologic Findings  
 Pathologic Physiology

Clinical Picture  
 Laboratory Findings  
 Diagnosis  
 Treatment  
 Response to Therapy  
 Prognosis

**Definition.** Sprue is a syndrome characterized by glossitis, steatorrhea, and other evidences of malabsorption, loss of body weight, macrocytic anemia accompanied by moderate leukopenia,

and megaloblastic arrest of the marrow. Free gastric hydrochloric acid is usually present; neurologic changes are rare. The disease is most frequently encountered in individuals with a

history of a monotonous, relatively low-protein dietary, particularly unsatisfactory in its content of sources of animal protein.

**Classification.** Much confusion exists concerning the identity of sprue, tropical sprue, non-tropical sprue, idiopathic steatorrhea, celiac disease, and related syndromes. The position is clarified by breaking down the syndrome as follows: Primary sprue, frequently termed tropical sprue, exhibits numerous characteristics of a deficiency disease and may, in fact, be regarded as resulting from a deficiency of one or more of the newer hemopoietic vitamins (pteroylglutamic acid, vitamin B<sub>12</sub>, or other "animal protein factors"). If the deficiency be sufficiently prolonged, irreversible changes may occur in the gastrointestinal tract, giving rise to partially or totally resistant primary sprue. Secondary sprue or idiopathic steatorrhea may develop quite independent of any deficient diet and as a result of pathologic changes in the gastrointestinal tract or mesentery. Secondary to and conditioned by the malabsorption resulting from such changes, any of several deficiency states may be manifest, including a lack of hemopoietic vitamins. Accordingly, a partial clinical response is obtained when these therapeutic agents are administered, and it may be exceedingly difficult to differentiate between such a patient and one with partially resistant primary sprue.

Gastrointestinal defects occurring in celiac disease in infants resemble those encountered in sprue in adults, and it is often held that the two syndromes are identical. Most infants with celiac disease, however, do not exhibit hematologic findings of a macrocytic anemia, and their general response to therapy with hemopoietic agents is less dramatic than is that of the patient with sprue. The constitutional defect in celiac disease has been emphasized, and it is probable that the occasional patient who exhibits macrocytic anemia and steatorrhea should be considered as suffering from a secondary deficiency of the principle(s) found in liver extract.

In the present discussion, emphasis will be given to a consideration of primary sprue as here conceived.

**Etiology.** The exact etiology of sprue cannot be stated. It appears not unreasonable to consider that the disease results from a lack of one or more of the hemopoietic vitamins (the pteroylglutamates, vitamin B<sub>12</sub>, or "animal protein fac-

tors"). As with many deficiency diseases, there may well exist a constitutional factor which renders an individual more susceptible to the development of the deficiency. It is of interest that its development is often associated with the later period of pregnancy. The possible role of an infectious agent has not been excluded, particularly in those instances where the disease suddenly appears as an epidemic. Some experimental findings would be consistent with an hypothesis relating the disease to changes in the flora of the gastrointestinal tract. The experimental analog of the disease appears to be the vitamin M-deficient monkey.

**Occurrence and Epidemiology.** Sprue is more prevalent in southeastern Asia, China, India, and the Malayan Archipelago, and in Puerto Rico and Cuba of the West Indies than in some of the other tropical or semitropical areas. Outbreaks of sprue in epidemic proportions have been noted in military personnel in India and Burma. The disease occurs with less frequency in the southern United States and is infrequently encountered in the northern portion of the country, except where cases are imported to medical centers. In the northern United States, those cases classified as "sprue" seem very frequently to be examples of secondary sprue or idiopathic steatorrhea.

**Pathologic Findings.** The pathologic findings in sprue are primarily those attributable to starvation and emaciation. Great variation exists in the pathologic changes of the gastrointestinal tract as described at autopsy. This may be due to the variety of conditions included under the diagnosis of the sprue syndrome. Varying degrees of thinning and irregular dilatation of the intestinal wall may be seen. Atrophy of the intestinal mucosa and of the tunica muscularis, with or without round-cell infiltration of the gut wall, is common. Deposits of brownish pigmentation similar to that observed in vitamin E-deficient animals have been noted in the wall of the gastrointestinal tract. Degeneration of nerve cells in the myenteric and submucosal plexuses has been described in sprue—a finding which has been noted on several occasions in monkeys on diets which were most probably deficient in vitamin M.

The bone marrow shows hyperplasia of the erythrocytic series with a predominance of younger cell forms, including megaloblasts—a picture indistinguishable from the megaloblastic hyperplasia which is observed in pernicious ane-

mia. As in the latter disease, there is also a shift toward the younger forms of the leukocytic series. These changes do not occur in the absence of anemia.

A great variety of changes in the gastrointestinal tract may give rise to secondary sprue—lymphosarcoma, amyloid disease, intestinal lipodystrophy (Whipple's disease), tuberculosis, etc.

**Pathologic Physiology.** In reversible primary sprue the gastrointestinal defects, as well as hematologic findings, both respond to a single pure therapeutic agent, folic acid. Malabsorption from the gastrointestinal tract in these cases may, therefore, be considered as a result of a deficiency of this vitamin. Impairment of absorption of both water- and fat-soluble substances occurs. These are but relative changes, inasmuch as a considerable portion of both water-soluble and fat-soluble materials do pass the intestinal barrier. The amount lost, however, is sufficient to bring about a significant decrease in total nutrients available to the body. For example, the loss of 50 Gm. of fat in the stool per day represents a fecal loss of 450 calories. Dissolved in this unabsorbed fat are quantities of lipid-soluble materials, such as vitamins A, K, and D, carotene, and tocopherols. If the dietary intake of these factors be low, there may result secondary deficiencies. In some cases, long-continued defective absorption of vitamin D impairs calcium absorption sufficiently that significant lowering of serum calcium levels and tetany may result. The impaired absorption of calcium is often stated to be due in part to the formation of sparingly soluble calcium soaps due to the presence of excessive quantities of split fat in the stool.

Absorptive defects may reduce the available supply of water-soluble vitamins to such a level that clinically manifest secondary deficiencies of these nutrients occur. Such secondary deficiencies are, in the writer's experience, encountered more frequently in idiopathic steatorrhea or sprue secondary to primary gastrointestinal disease.

**Clinical Picture.** Diarrhea, indigestion, flatulence, abdominal distention, soreness of the tongue or mouth (Fig. 95), weight loss, and weakness are the most common symptoms. The drawing, or cramping, of tetany is occasionally a complaint. Anorexia may or may not be present. The onset of symptoms may have been gradual or acute, and the history may date for a period of from weeks to years. Cases of longer duration

may have undergone periods of remissions and exacerbations.

The dietary history most frequently indicates a monotonous, restricted intake low in protein-containing foods of higher biologic values.



FIG. 95. Appearance of the tongue (A) before treatment; (B) three weeks after first treatment. Papillary regeneration of about this extent had been apparent approximately two weeks earlier. (Courtesy, Darby, Jones, and Johnson: J.A.M.A., 130:780, 1946.)

The typical patient is a pale, rather emaciated individual with dirty brownish pigmentation over the neck, face, and hands. Atrophy of the lingual papillae and some increased redness of the tongue are usually observed. Aphthous stomatitis may be present. Pellagraform lesions, petechiae, mild dependent edema, and signs of tetany may be noted. Hypotension is the rule.

The characteristic stool is light in color, soft, liquid to semiliquid in consistency, greasy appearing, and foul smelling, and tends to float in water. In an occasional patient, however, the stool may not have these characteristics, but may be a greasy, though well-formed, rather dark-colored stool.

**Laboratory Findings.** The anemia may be of any degree of severity. In primary sprue, it is almost always macrocytic in character. There may coexist a moderate leukopenia and thrombocytopenia. The appearance of the stained blood film is identical with that seen in pernicious anemia. Aspirated bone marrow is found to be hyperplastic, with an increase in the numbers of the erythrocytic series and a preponderance of immature cells. Megaloblasts are present in numbers somewhat proportional to the degree of the anemia. In the peripheral blood of the untreated patient, the reticulocytes may vary from less than 1 per cent to as high as 6 or 8 per cent. Histamine-fast achlorhydria is found in only about 30 to 40 per cent of the patients. An in-

Increase in fecal fat is generally agreed to be the *sine qua non* of sprue. The most reliable criterion for judging impairment of fat absorption is a six-day metabolic balance. Loss of more than 10 per cent of ingested fat can, with certainty, be taken as evidence of steatorrhea. Where this procedure is impossible, the finding that more than 25 to 30 per cent of the dry weight of the stool is fat is useful evidence in favor of steatorrhea. If the diet contains carotene, extraction of the feces with fat solvents reveals considerable quantities of this pigment.

X The oral glucose tolerance curve is flat (i.e., exhibits a maximum rise of less than 40 mg. %); the Intravenous glucose tolerance curve, on the other hand, does not differ from normal. The serum carotene level and plasma tocopherols are almost invariably low; vitamin A levels may or may not be decreased. X Vitamin A tolerance curves, following ingestion of 200,000 I.U. of vitamin A, are flat. Cholesterol values are usually lower than normal. Slightly low serum proteins are not infrequent. Serum vitamin C levels and urinary excretion of B-complex vitamins are usually low. Serum calcium levels may or may not be decreased. Prothrombin time frequently is abnormally prolonged.

X Roentgenologic abnormalities of form and movement of the small intestines are characteristic of sprue but not pathognomonic of the disease. These changes may consist of hypomotility and hypertonicity in the earlier stages, and hypomotility and dilatation in advanced stages. Segmentation of the barium into smooth, dilated, sausage-like segments occurs, particularly in the jejunal loops. This appearance gives rise to the so-called "moulage" sign—the appearance of a tube into which wax has been poured. (Coarsening of the mucosal folds) in the duodenum and upper jejunum is a frequent finding. Demineralization of the skeletal system may be evident.

**Diagnosis.** The diagnosis of the sprue syndrome is made from the history, physical findings, hematologic studies (including examination of the marrow), and laboratory and roentgenologic findings. Of particular value is the chemical determination of stool fat (preferably a six-day balance study), serum carotene level, glucose and vitamin A tolerance tests, and determination of gastric acidity.

The differentiation of primary from secondary

sprue may be exceedingly difficult, but a finding of a definite disease process of the gastrointestinal tract makes virtually certain the diagnosis of secondary sprue. Of considerable importance in the differentiation of these two entities is recognition that the degree of anemia is usually less in secondary sprue than in primary, and, accordingly, the megaloblastic hyperplasia of the marrow may be slight or absent in the secondary sprue. Glossitis is usually mild or absent in the secondary disease, while tetany is encountered more frequently.

Differentiation from pernicious anemia rests upon the complete achlorhydria in this disease and the demonstration of the pronounced absorptive defects which are present in sprue and absent in pernicious anemia. The occurrence of combined system disease favors the diagnosis of pernicious anemia.

Distinction from so-called "nutritional macrocytic anemia" is difficult and probably only a matter of degree. In general, nutritional macrocytic anemia resembles primary sprue, except for the mildness of the absorptive defects. In nutritional macrocytic anemia, steatorrhea is not pronounced. "Pernicious anemia of pregnancy" is not accompanied by such profound changes in absorptions, and responds most satisfactorily to folic acid. When a remission is induced by treatment following delivery, continued maintenance therapy is not required. Pancreatic steatorrhea, especially in children, may closely simulate the picture of sprue. It is, however, associated with increased fecal nitrogen, decreased concentration of digestive enzymes in duodenal juice or feces, a normal or diabetic type of glucose tolerance curve, and, ordinarily, a less severe degree of anemia.

The differentiation of sprue from pellagra usually is not difficult. The two diseases may coexist. Superficially, the resemblance to Simmonds' disease, anorexia nervosa, general cachexia of malignancy, and Addison's disease may be confusing. Appropriate studies serve clearly to distinguish the syndromes.

Roentgenologic and sigmoidoscopic studies assist in differentiation of sprue from tuberculous enteritis, from regional enteritis, and from idiopathic ulcerative colitis.

**Treatment.** The treatment of primary sprue consists of the administration of an active specific nutritional entity (folic acid, liver extract, or

vitamin B<sub>12</sub>); the provision of an abundant high-protein, moderately low-fat diet; and supplementation with appropriate amounts of other nutritional factors of which there is a demonstrable deficiency. In some instances, this latter may be the most urgent therapeutic procedure. For example, when hemorrhage is occurring as a result of hypoprothrombinemia in sprue, the administration of vitamin K is a medical emergency.

Final appraisal of specific therapeutic agents cannot be made at the time of writing. In the author's experience, 5 to 20 mg. of folic acid per day, orally or parenterally, has resulted in very satisfactory remissions. Large doses of parenteral liver extract (usually crude) also provide satisfactory therapeutic results. However, some reports suggest that the occasional case of sprue responds somewhat better to administration of folic acid than of liver extract. On the other hand, at the Vanderbilt Hospital, we have observed two patients with sprue who, following good initial responses to folic acid and satisfactory maintenance for up to two and one-half years, experienced a hematologic relapse which subsequently responded to administration of vitamin B<sub>12</sub>. At this time, only preliminary reports are available concerning the effectiveness of vitamin B<sub>12</sub>, and, accordingly, the completeness of the response to this agent cannot be evaluated. Some form of specific maintenance therapy is usually necessary in cases of sprue, unless drastic and permanent changes can be brought about in the dietary pattern.

Therapy of patients with resistant primary sprue or with secondary sprue is much less satisfactory. Response to specific therapeutic agents in these conditions is not complete, and, at times, no response whatsoever is obtained. The administration of an emulsifying agent, such as "Tween 80" or lecithin, may be of value in promoting the absorption of fat and lipid soluble materials. The use of "Tween 80" in doses of 1.5 Gm. three times a day has been recommended. The final place of such therapeutic agents has not been defined.

The ~~x~~ complication of tetany may usually be controlled by intravenous administration of 10 per cent calcium gluconate followed by oral dosing with calcium chloride and vitamin D. Administration of supplementary vitamin A is indicated in the rare case in which there is night blindness or some other manifestation of avitaminosis A.

**Response to Therapy.** The administration of a specific agent to patients with primary sprue is followed by prompt and gratifying hematologic and clinical improvement. The symptoms of glossitis disappear within two to four days, and this is followed by rapid regeneration of lingual papillae. An improved sense of well-being is noted within two or three days. The diarrhea subsides usually within a week, the appetite improves to the point of ravenousness, and weight gains of a pound per day are not unusual. In the rapidly gaining patient, there frequently occurs a temporary edema which subsides without additional therapy by the end of the second or third week of treatment.

The first evidence of hematologic remission is a reticulocytosis which follows the pattern observed in treated pernicious anemia. Hematologic response following administration of folic acid to a patient with sprue is depicted in figure 96.

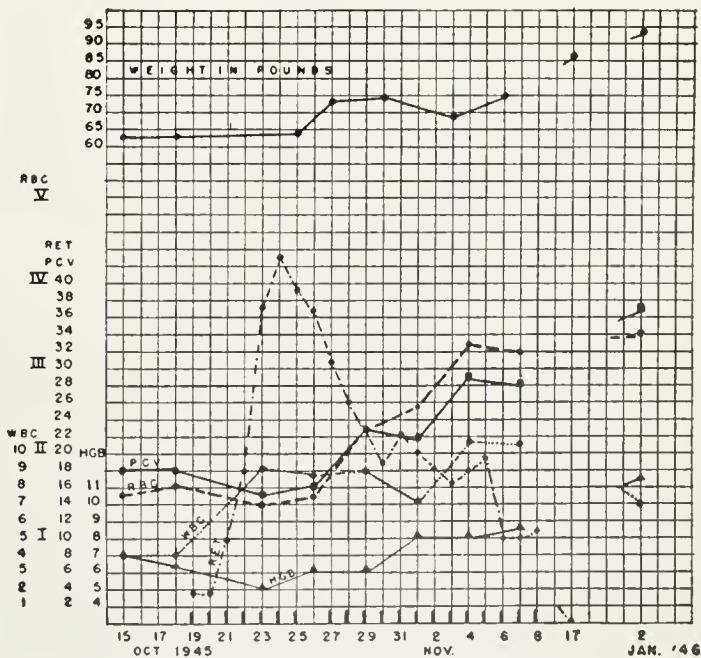


FIG. 96. Hematologic responses to treatment. Each upright bar represents the intramuscular injection of 15 mg. of synthetic *Lactobacillus casei* factor. Weight changes are shown at the top. (Courtesy, Darby, Jones, and Johnson: *J.A.M.A.*, 130:780, 1946.)

Within two weeks to a month, there is usually an increase in the maximum rise of the glucose tolerance curve. After several weeks of therapy, there usually occurs an increase in the serum carotene and tocopherol levels and a slow return of the vitamin A tolerance to normal. Simultaneously, the roentgenologic pattern of the gastrointestinal tract may slowly revert toward normal. In the most favorable case, all of these changes

occur. One or another of these responses, however, may be absent or but partial in a given situation. Specific hemopoietic agents have little effect on those symptoms of secondary sprue which are primarily manifestations of impaired absorption.

**Prognosis.** The prognosis is good in primary sprue. Approximately 1 to 6 per cent of the patients are resistant to specific therapy at the time they are first seen. Some tendency toward the recurrence of gastrointestinal symptoms is encountered not infrequently in those cases of long standing.

In secondary sprue, the prognosis obviously depends upon the degree of injury to the gastrointestinal tract and the progressiveness of the primary lesions. In general, the control of the patient is less satisfactory than in the primary disease, and he may seldom become completely symptom-free.

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## Carotenemia

William J. Darby

Strictly defined, the term *carotenemia* means the presence of excess of carotene in the blood. Excess of carotenoid pigments in the blood is often associated with deposits of pigments in the skin, so-called "aurantiasis cutis." Accordingly, the term *carotenemia* is widely used to designate the state of hypercarotenemia with associated yellowish discoloration of the skin due to the deposition of carotenoid pigments.

Carotenemia is encountered most frequently in infants whose diets have constantly included an abnormally large amount of yellow vegetables and fruits and green vegetables. These diets are usually noteworthy for their high content of carrots, spinach, apricots, peaches, oranges, and yellow squash. The disease also occurs in adults who have maintained a constantly high intake of such pigmented fruits and vegetables, especially carrots.

Carotenemia is revealed by an asymptomatic yellowish discoloration most marked on the palms, soles, forehead, and chin, in the nasolabial grooves, behind the ears, and over the knuckles. In severe cases, the whole body surface may be tinged. This distribution is in contrast to that seen in jaundice, where the discoloration is usually most intense on the chest and least on the hands and feet. Carotenemia is differentiated from icterus by the complete absence of discoloration of the sclerotics in carotenemia. The urine may be amber in color. The serum level of carotenoids is found to exceed approximately 500 I.U. (300 µg.) per 100 ml. in most cases, although some pigmentation may be observed at slightly lower levels. Carotenemia has long been associated in the mind of the clinician with diabetes, inasmuch as it has been noted frequently in this disease. A factor in the occurrence of carotenemia in diabetes has been the large

quantity of pigment ingested by the diabetic. Some evidence indicates, however, that the occasional diabetic may have difficulty in converting carotene into vitamin A, and this impairment may influence the development of carotenemia in the disease. Carotenemia is not infrequently associated with increased serum lipids and hypercholesterolemia.

The clinical importance of carotenemia is threefold: (1) The condition must be differentiated from jaundice—a differentiation which rests upon history; upon the absence of discoloration of the sclerae in carotenemia; upon a normal icterus index (following acetone precipitation) and van den Bergh reaction in carotenemia, coupled with a high level of serum carotene; and upon the presence or absence of those physical findings associated with conditions which may give rise to jaundice. (2) In rare instances, carotenemia may call attention to unrecognized diabetes or nephrosis. (3) Carotenemia may be a reflection of a rather bizarre dietary pattern which should be explored by the physician.

The treatment of carotenemia consists of temporary exclusion from the diet of those foods which are rich sources of carotene, such as the green and yellow vegetables, yellow fruits, and the like. Following such exclusion, the serum carotene levels gradually fall and pigmentation lessens over a period of several weeks.

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## General Considerations

George W. Thorn and Peter H. Forsham

Endocrinology may be defined as the study of the glands of internal secretion. As a science it is barely 100 years old, the cornerstone having been laid in 1849 by Berthold, who observed that the effects of castration in the fowl were abolished by the implantation of testicular tissue. Thomas Addison, in 1854, drew attention to the existence of a fatal syndrome associated with the destruction of the adrenal glands. Brown-Séquard, in 1889, then an old man, stimulated widespread discussion and experimentation following his claim that the injection of testicular extracts from animal sources exerted a rejuvenating effect upon him. It was not until 1904, however, following the discovery by Bayliss and Starling of "secretin," a humoral substance capable of initiating the flow of pancreatic juice, that endocrine secretions received their now accepted designation as hormones. This generic term, which connotes an "exciting substance" or "messenger," soon included a large number of biologically active glandular principles.

The greatest advances in endocrinology followed upon those of neurophysiology and clearly demonstrated that integration of function was not dependent exclusively on the nervous system. The recognition of the general importance of the humoral transmission of nervous impulses reduced endocrine and neural regulation of function to a common mechanism involving the action of diffusible substances—mediators or hormones—on tissue cells or end organs.

Until specific hormones were recognized, isolated, and purified, endocrinology was largely a descriptive discipline. Thus far, four types of hormones have been recognized chemically: (1) large protein molecules, of which insulin and pituitary gonadotrophins are examples; (2) polypeptides, such as posterior pituitary hormones and adrenocorticotrophin; (3) aromatic derivatives, such as thyroxin and epinephrine; (4)

steroid hormones, which include the adrenocortical and gonadal factors.

Hormones affect the rate of intermediate metabolism within certain cells, thereby controlling their function. Hormones may act by changing cellular permeability and intracellular organization or by affecting specific steps in intermediary metabolism. Endocrinopathies are, in essence, disorders of metabolism. Hormones do not initiate new metabolic activities within the cell, but merely enhance the efficiency of reactions.

Classic methods of investigating the function of the endocrine glands include: a study of the signs and symptoms of patients suffering from deficiency or excess of a particular hormone; experiments in which a deficiency of the gland is produced by destruction or extirpation; or experiments in which excessive hormonal action is attained by stimulation of the gland or by massive substitution therapy. With the availability of pure hormones, their effect on cell mechanisms could at last be studied in detail.

Hormonal secretion may be regulated by the central nervous system directly, by secretion of other hormones, or by changes in the internal environment. The endocrine glands constitute organs which possess a definite functional reserve which may be impaired if understimulated or overstimulated.

Because it may involve many organs, an endocrinopathy is usually not a clear-cut pathologic entity. This is so because some of the fundamental chemical processes modified by hormonal action may be common to many body tissues. Since the ultimate manifestation of disordered hormone secretion is reflected in abnormalities of cellular function, it is possible for disturbances in neural mechanisms, essential cell constituents, or genetic or structural abnormalities in the cell to simulate endocrinopathies.

Endocrine disorders based upon abnormal

function of the glands of internal secretion represent an increasingly important field of medicine. This fact is due to the realization not only of the importance of specific hormonal disturbances, but also of the widespread action of hormones in modifying nonendocrine systemic diseases. Important examples of the latter type of action are illustrated by the remarkable effect of the adrenal cortical steroids in diseases such as rheumatoid arthritis, the use of insulin in shock therapy, and the effect of estrogens in the treatment of prostatic cancer.

For convenience one may divide the glands of internal secretion into two general categories: (1) the anterior pituitary and its satellite group of "target glands" which include the thyroid, adrenal cortex, gonads, and to some extent the pancreatic islet tissues; and (2) the posterior pituitary, parathyroid, and adrenal medulla. Except for the growth hormone, the secretions of the anterior pituitary do not initiate any important change other than those mediated through their respective target glands. The functional integrity of the adrenal cortex, thyroid, and gonads is under direct control of the respective trophic hormones emanating from the anterior pituitary gland under neurohumoral stimulation. The blood level of adrenal cortical, thyroid, or gonadal hormones appears to be an important regulating factor in the secretion of the specific pituitary trophic hormone. The activity of the posterior pituitary glands, the parathyroid, and the adrenal medulla appears to be mediated either by stimuli occurring in the blood and other body fluids, or by stimuli arising in the nervous system.

As an example of perfect physiologic integration, the studies of Cannon, Selye, and Long are of interest. Epinephrine and other substances, liberated in response to stress or injury, appear to stimulate sensitive end organs in the hypothalamus. These in turn secrete a substance which is thought to be transmitted humorally to the anterior pituitary where it activates the secretion of pituitary adrenocorticotrophin or ACTH. The response of the adrenal cortex to an increased secretion of its trophic hormone results in the liberation of large quantities of adrenal steroids, so essential to the maintenance of homeostasis.

These observations provide some indication of the widespread nature and importance of the hor-

mones in health and disease. These studies have cast considerable light on the basic nature of hormonal response to such divergent disturbances as acute infections, circulatory disorders, and emotional states. Indeed, it is apparent now that, without the application of any medication, psychologic or emotional stimuli may initiate the series of important reactions which lead to pituitary-adrenal activation with consequent widespread changes in the body.

In approaching a patient with a metabolic or endocrine abnormality, one proceeds initially as with the investigation of any patient. Certain features, however, should be stressed. In eliciting the history, one should inquire particularly concerning changes in body weight and in the rate of growth; the age of onset of puberty and menstruation; the presence or absence of weakness and fatigue; changes in hair, skin, and nails; and changes in libido and potency, as well as any alteration in reaction to changes in physical environment or emotional and psychologic stress. The number of serious illnesses, their sequelae, and above all the capacity of the patient to return to normal life following a serious illness are of great assistance in estimating the integrity of the endocrine system. Fatigue coming on in the evening after a day's work is more likely organic in nature than that which is exhibited in the morning on arising and which may tend to disappear toward evening. Undue concern over diminished libido and potency almost invariably distinguishes the hormonally intact but disturbed patient from the hypogonadal male who is relatively undisturbed by his impotence and may have sought the physician's aid because of blurred vision due to a pituitary tumor.

In the physical examination one should note particularly the body build and fat distribution; the character and quality of the hair, skin, and nails; pigmentation; abnormalities in bones and muscles; development of the gonads, breasts, and secondary sex characteristics; anemia or plethora; dehydration or edema; hypotension or hypertension; pulse rate; and general attitude.

There are a few chemical determinations which are of particular value in the detection or differentiation of endocrine disorders: (1) fasting and postprandial blood sugar; (2) serum calcium, phosphorus, and phosphatase levels; (3) serum sodium, potassium, and carbon dioxide values;

and (4) serum cholesterol. Excessive blood sugar levels under fasting circumstances are suggestive of diabetes mellitus or hyperadrenocorticism (Cushing's syndrome); low blood sugar levels generally are found in hyperinsulinism, adrenal cortical deficiency, or hypopituitarism. Disturbances in serum calcium, phosphorus, and phosphatase levels occur in disease of the parathyroid glands, in acromegaly, and in Cushing's syndrome. Abnormalities in serum sodium, potassium, and chloride occur in disturbances of the adrenal glands. High cholesterol levels occur characteristically in hypothyroidism and diabetes.

Among other laboratory examinations of considerable aid are the determination of the basal metabolic rate in patients with thyroid and pituitary disturbances; x-ray films of the body skeleton in patients with thyroid, pituitary, or parathyroid disease; and the specific response to administration of trophic hormone such as adrenocorticotrophin, thyrotrophin, and gonadotrophin. It is also possible to measure directly

certain hormonal constituents or their excretion and degradation products, such as the protein-bound iodine of the serum, urine or blood gonadotrophins, estrogens, progesterone, antidiuretic hormone, urinary corticoids, and 17-ketosteroids. It is not practical to measure parathyroid hormone, insulin, or epinephrine. The principal difficulty in integrating the values obtained in these measurements lies in the wide cyclical variations which glandular secretions undergo in normal life.

Endocrinologic disease offers a challenge to the physician by combining specific signs with measurable metabolic and hormonal changes. In addition, many of the endocrine diseases are amenable to adequate substitution therapy, and in some cases a permanent cure may be effected. In the last analysis the diagnosis of endocrine disease is made by combining clinical experience with the results of laboratory tests, either of which alone is often insufficient for an adequate appraisal of the patient.

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### Diseases of the Anterior Pituitary Gland

George W. Thorn and Peter H. Forsham

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#### INTRODUCTION

Diseases of the anterior pituitary gland may be differentiated into those related to an altered secretion of one or more of the several hormones liberated by the gland. In many instances, these

alterations are due to pressure changes in and about the pituitary, associated with tumors, inflammations, infection, or vascular changes.

To Lorain, in 1871, must go the credit for suspecting a causal relationship between hypophyseal lesions and dwarfism. Pierre Marie described acromegaly in 1886, but Minkowski, one year later, was the first to recognize a causal relationship between the hypophysis and the disease. Simmonds, in 1914, advanced clinical understanding of pituitary function by describing a peculiar type of cachexia which followed post-partum thrombosis of the pituitary gland. The studies of Paulesco, Cushing, Aschner, Cannon, P. E. Smith, and B. M. Allen showed that hypophysectomy exerted a marked effect on growth and other metabolic processes.

The experiments of H. M. Evans in 1921 conclusively proved that the anterior lobe of the hypophysis contained a growth-promoting hormone. Subsequently it was shown that, in addition to its growth-promoting propensity, the anterior hypophysis stimulated the development of the gonads, thyroid, and adrenals. P. E. Smith in America, in 1926, and B. Zondek in Germany discovered that pituitary implants introduced into immature rats produced precocious ovarian development due to the presence of gonadotrophin. Later studies revealed the existence of two gonadotrophins—one stimulating follicle maturation (FSH) and the other stimulating luteinization of existing follicles (LH or ICSH).<sup>1</sup> Of relatively recent origin are studies indicating that in the male FSH stimulates spermatogenesis and LH stimulates Leydig cell formation. The luteinizing hormone, prolactin, corticotrophin, growth hormone, and follicle-stimulating hormone have been isolated in highly pure form; thyrotrophin has been prepared in relatively pure form. Other hormones are present in the anterior pituitary, but their identity has not been established.

In the early experimental work on the hypophysis, considerable confusion arose regarding the interpretation of changes relating to the pars anterior and pars nervosa. Oliver and Sharpey-Schafer in England, in 1894, observed that posterior pituitary extracts exerted a vasoressor action in experimental animals. A. E. Frank, in 1912, suggested that a hypophyseal lesion was probably the cause of polyuria in patients with diabetes insipidus. Kamm, in 1928, succeeded in separating posterior lobe extract into vasoressor and oxytocic factors. The anti-diuretic principle of posterior pituitary extracts is probably identical with the vasoressor one. Diabetes insipidus was first clearly differentiated from diabetes mellitus by Willis in 1670. Von den Velden and Farini, in 1913, successfully treated the disease with posterior pituitary preparations.

In 1932 Cushing described the syndrome now named after him and thus emphasized clinically

the widespread metabolic effects of anterior pituitary dysfunction.

Recent purification of several of the anterior pituitary hormones in quantities adequate for clinical studies has permitted an intensive investigation of their particular metabolic effects.

Histologic studies reveal that the anterior pituitary contains three types of cells—i.e., chromophobe, eosinophil, and basophil. The cytologic origin of the anterior pituitary hormones has not been determined definitely. In pathologic conditions associated with eosinophilic tumors there appears to be increased secretion of growth, luteinizing, lactogenic, and occasionally thyrotrophic hormones; while in basophilic tumors the follicle-stimulating and adrenocorticotrophic hormone secretions are usually elevated. The chromophobe cells, which are considered to be the precursors of the other two cell types, do not secrete hormones. Most of the activity of crude anterior pituitary extracts may be accounted for by one or more of the constituent trophic hormones.

Growth hormone increases the rate of skeletal growth and induces a gain in body weight. It also tends to inhibit the action of insulin. Adrenocorticotrophin appears to stimulate all of the known hormonal groups of adrenal cortical steroids and induces adrenal cortical hypertrophy. Thyrotrophin induces hyperplasia of the thyroid gland, stimulates the synthesis of thyroid hormone, and accelerates its release into the circulation. Follicle-stimulating hormone stimulates the growth of Graafian follicles and aids in estrogen production. It is also essential for spermatogenesis, stimulating the seminiferous tubules of the testes. The luteinizing hormone (LH) is necessary for ovulation and corpus luteum formation in the ovary. It stimulates the production of both estrogen and progesterone. In the male, LH stimulates the testicular Leydig cells and leads to the formation of testicular androgens. Lactogenic hormone, luteotrophin (LTH), maintains the corpus luteum of pregnancy, stimulates progesterone formation, and is essential for mammary gland development and lactation.

The production and secretion of anterior pituitary hormones is modified by the serum level of hormones produced in response to pituitary trophic hormone action. For example, increased circulatory thyroid hormone appears

<sup>1</sup> Throughout the text we use the initials "LH" to denote the luteinizing hormone, both in the female and in the male, although in the latter the terminology "interstitial cell-stimulating hormone" (ICSH) would be more accurate. The hormone appears to be chemically the same in both sexes, and uniform terminology will avoid confusion.

*Table 50*  
HORMONES OF THE ANTERIOR PITUITARY

Hormone	Source	Nature	Molecular Weight*	Isoelectric Point	Sulfur Content (%)
Adrenocorticotrophin (ACTH)	Sheep; hog	Protein	20,000	4.7	2.3
Growth hormone (somatotrophin; GH)	Beef	Protein	44,250	6.85	1.3
Thyrotrophic hormone (thyroid-stimulating hormone; TSH) (impure)	Beef; sheep; horse	Glycoprotein	10,000	4.1	1.0
Follicle-stimulating hormone (FSH; prolactin-A; thytlakentrin)	Sheep; hog	Glycoprotein	70,000	4.5	..
Luteinizing hormone (LH; interstitial cell-stimulating hormone; ICSH; metakentrin)	Sheep	Glycoprotein	40,000	4.6	..
Luteotropic hormone (LTH; lactogenic hormone; prolactin)	Hog	Glycoprotein	100,000	7.45	..
	Beef; sheep	Protein	32,000	5.7	1.8

\* Approximate only.

to depress the further secretion of pituitary thyrotrophic factor.

Recently it has been shown that epinephrine is capable of stimulating the anterior pituitary to liberate increased quantities of adrenocorticotrophin, luteinizing hormone, follicle-stimulating hormone and thyrotrophin. Stimulation of the hypothalamus appears to be a necessary pathway for this phenomenon. It appears certain, however, that hypothalamic stimuli arising in response to anxiety, exposure to stress, etc., are capable of stimulating increased pituitary secretion. It is also probable that the dietary intake and nutritional status are important in regulating the type and quantity of anterior pituitary hormone secretion.

The anterior pituitary hormones are protein in nature. The present state of knowledge with respect to the chemical characterization of the known constituents is summarized in table 50.

As might be expected from the number of hormones liberated by the anterior pituitary, there are a large number of possible combinations of disturbances in secretory activity. Improvement in hormonal diagnostic tests and the availability of purified preparations of the individual pituitary hormones will permit much more exact classification of the types of dysfunction. At present one is able to classify accurately only those syndromes reflecting widespread pituitary insufficiency or excess; or the purer syndromes in which one hormonal disturbance predominates and characterizes the clinical picture. There are also a number of syndromes classified among diseases of the pituitary for which there is little

physiologic or pathologic evidence to justify their inclusion.

The protein nature of the majority of these hormones and their capacity for inducing an antibody response limit their use at present almost exclusively to diagnostic procedures. Thus, in practice, a deficiency of anterior pituitary trophic hormone may be corrected satisfactorily only by replacing the hormone or hormones liberated by the target gland—i.e., thyroid and gonads. Adrenocorticotrophic hormone seems to be an exception to the rule (see Disturbances in Adrenocorticotrophin Secretion, p. 557).

## GENERALIZED ANTERIOR PITUITARY DYSFUNCTION

### PANHYPOPITUITARISM

**Prepubertal—Lorain-Levi Syndrome.** In 1871 Lorain first pointed out the syndrome of dwarfism or infantilism associated with destructive lesions of the hypophysis. Prepubertal panhypopituitarism is a very rare condition usually associated with a suprasellar cyst or craniopharyngioma. The disease is characterized by dwarfism and subnormal sexual development. Mentality is normal. The impairment in growth is symmetric, and the body proportions are normal. The hands and feet are small; the skin is dry, yellowish, and wrinkled. Weight loss is minimal. Sexual maturation is delayed. The appearance of precocious senility which may be present is due in part to the looseness of the skin, which is deficient in subcutaneous fat. If the hypothalamus is involved, there may be obesity. If the optic

chiasma is involved, there may be bitemporal or complete blindness. The basal metabolic rate is generally normal. X-ray studies indicate ununited epiphyses. Destruction of the sella turcica is frequently observed. Diagnosis depends chiefly upon clinical data and evidence of multiple "target" gland deficiencies. The availability of potent preparations of the various trophic hormones and the development of functional tests based upon the effects of these hormones will very likely permit more accurate diagnosis and evaluation of these cases.

The condition may be distinguished from genetic dwarfism and from hypothyroidism by the appearance of senility and the subnormal sexual development; and from achondroplasia by the normal body proportions.

Since, in the majority of instances, the disease is due to involvement of the pituitary by tumor or infection, the outlook depends to a considerable extent upon the nature of the primary disease. The hormonal deficiency cannot be corrected by anterior pituitary extracts because of the lack of availability of potent preparations and the distinct tendency of these protein preparations to form antibodies on continued administration. Trial with estrogens, testosterone, adrenal cortical extract, and thyroid is justified. The type of hormone and the quantity will depend upon an estimation of the relative deficiency of each of these satellite glands (see Simmonds' Disease, below). A few of the patients who present a clinical picture suggestive of pituitary dwarfism respond well to thyroid administration alone. In these cases, the condition is probably one of primary thyroid or of thyrotrophin deficiency alone, rather than of true panhypopituitarism.

**Postpubertal.** For practical purposes patients with panhypopituitarism may be classified according to the severity or according to the etiology of the hypopituitarism. Availability of pure trophic hormones will undoubtedly permit a more precise classification.

1. **SIMMONDS' DISEASE.** In 1914 Simmonds described a case of post-partum necrosis of the pituitary with marked cachexia. He correlated his clinical-pathologic findings with Paulesco's experimental observations on the profound effects of hypophysectomy. The term "Simmonds' disease" is usually reserved for cases characterized by marked insufficiency of the "target" glands resulting in profound cachexia.

**ETIOLOGY.** Post-partum pituitary necrosis due to thrombosis appears to be the most common cause of this syndrome. Pituitary tumors, craniopharyngiomas, and occasionally brain or vascular tumors may cause atrophy of the gland by pressure, or the function of the gland may be impaired following x-ray therapy. Brain injuries and granulomatous infections are rarer causes of the syndrome.

**PATHOLOGY.** Marked atrophy or destruction of the anterior pituitary is observed, with secondary atrophy of the thyroid, adrenals, and gonads. Very few of the anterior pituitary cells persist, and most of these are chromophobe. Since in the majority of instances the disease occurs post-pubertally, skeletal growth is not affected. The cachexia and progressive weight loss are compatible with negative nitrogen balance secondary to pituitary growth hormone deficiency.

**INCIDENCE.** The disease is rare. In 1942 Escamilla was able to collect 595 cases from the literature, with only 101 cases proved pathologically and 158 with a characteristic clinical picture.

**CLINICAL PICTURE.** The symptoms of severe hypopituitarism in the adult are weight loss (frequently extreme), asthenia, lethargy, disorientation, loss of libido, impotence, amenorrhea without menopausal flushes, and intolerance to cold. Frequently the syndrome manifests itself after parturition with failure to lactate. The signs consist of cachexia, pallor, premature senility, loss of teeth, loss of axillary and pubic hair, wrinkling of the skin which is dry and yellowish in appearance, a slow pulse, a low blood pressure, and loss of secondary sex characteristics with atrophy of the genitalia and breasts.

**DIAGNOSIS.** Laboratory findings include hypochromic anemia, leukopenia with relative lymphocytosis and eosinophilia, hypoglycemia, decreased basal metabolic rate (minus 20 to minus 40 per cent), and often gastric anacidity. Serum cholesterol is usually normal but may be elevated in the presence of associated hypothyroidism. The 17-ketosteroid excretion and the serum level of protein-bound iodine (thyroid hormone) are low. There is extreme sensitivity to insulin. Skull x-rays may reveal destruction of the sella in cases associated with tumors arising from the pituitary or surrounding structures.

2. **SHEEHAN'S SYNDROME.** Recently Sheehan has extended these clinical observations to include a larger group of patients, many of whom

failed to show the severe degree of cachexia described by Simmonds but did display evidence of widespread depression of anterior pituitary functional activity.

Sheehan states that many cases of mild postpartum pituitary insufficiency are not detected. Following delivery these patients fail to lactate, and have amenorrhea. There is little weight loss. The skin, although not wrinkled, has a peculiar waxy cast. Occasionally patients with mild panhypopituitarism become pregnant. If pregnancy is completed, the original mild hypopituitarism may be cured by the hypertrophy of the pituitary remnant during pregnancy.

Occasionally cases of panhypopituitarism masquerade as myxedema (see "Pituitary Myxedema," p. 560). In another group of patients the presenting symptoms consist primarily of weakness, weight loss, and hypotension. These symptoms of adrenal cortical insufficiency overshadow those of thyroid and gonadal atrophy; hence these may be termed cases of "pituitary-adrenal cortical deficiency" (see p. 558).

**3. CHROMOPHOBE ADENOMAS.** Chromophobe adenomas of the pituitary deserve special mention because of their relative frequency as a cause of hypopituitarism. About two thirds of all pituitary adenomas and about one fifth of all intracranial tumors are chromophobe adenomas. Since they are nonsecretory, they produce symptoms only through pressure on the neighboring organs, including, of course, the pituitary itself. They can, therefore, produce any of the pictures of hypopituitarism previously described, with amenorrhea, impotence, and obesity, usually occurring early. In addition, there may be symptoms of increased intracranial pressure and destruction of the sella by x-ray (fig. 97). Roentgen therapy is recommended for the early case; in the presence of compression of the optic pathways or advancing disease, surgical intervention followed by irradiation will be required. Hormonal treatment depends upon an evaluation of the deficiencies which are present. *Preoperative preparation with adrenocorticotrophic hormone is essential in these cases* (see Treatment, p. 554).

**4. MISCELLANEOUS LESIONS.** A picture of panhypopituitarism may also be produced by other rarer lesions such as craniopharyngiomas, gliomas with invasion of the pituitary, and granulomatous infections. Tumors which lead to hyperpituitarism (e.g. eosinophilic adenomas with acromegaly,

or basophilic adenomas with Cushing's disease) may well give a picture of hypopituitarism as they evolve, either because of the "burning out" of the tumor itself or because of the results of x-ray treatment or surgery.



FIG. 97. Lateral skull x-ray of a 47-year-old female. A cystic chromophobe adenoma of the pituitary was found at operation. Note marked enlargement of the sella turcica and erosion into surrounding bone.

**Differential Diagnosis.** The weakness and cachexia suggest neoplasm or chronic infection. The low basal metabolic rate and the marked sexual atrophy differentiate Simmonds' syndrome from chronic infection. Neoplasm may be differentiated only by careful physical and roentgenologic examination. Since gonadotrophic, thyrotrophic (TSH), and adrenocorticotrophic (ACTH) hormones are available, it is relatively simple to differentiate between primary pituitary and primary "satellite deficiency" by a positive response to the trophic hormone in the case of pituitary failure (see "Pituitary-Adrenal Cortical Deficiency," p. 558; and Addison's Disease, Differential Diagnosis, p. 594).

Recently a simple test has been standardized which appears to be helpful in the diagnosis of pituitary insufficiency. It is based upon the principle that epinephrine is capable of stimulating

the anterior pituitary to liberate adrenocorticotrophin. The test is carried out as follows: 0.3 mg. of epinephrine is administered subcutaneously. Prior to the test, and four hours after it, the circulating eosinophils are counted directly (see Addison's Disease, Diagnosis p. 595). A fall of more than 50 per cent in circulating eosinophils indicates an intact anterior pituitary as far as ACTH production and release are concerned. A negative test (less than 50 per cent fall in circulating eosinophils) is of little help in diagnosing pituitary insufficiency, since this may be due to other causes such as secondary adrenal atrophy or allergic disease (see Addison's Disease, Diagnosis, p. 594). It may become possible to study TSH and FSH production by the same type of mechanism. The epinephrine test should not be used in patients with severe cardiovascular disease.

Primary gonadal deficiency does not present the constitutional changes characteristic of widespread anterior pituitary deficiency. The demonstration of normal or high FSH (follicle-stimulating hormone) concentration in blood or urine eliminates panhypopituitarism as a diagnostic consideration.

Anorexia nervosa constitutes the most common and most difficult differential diagnostic problem. Clinically, patients with anorexia nervosa may be more alert and active. The anorexia usually precedes the amenorrhea, in contrast to panhypopituitarism in which amenorrhea may precede by months other evidence of anterior pituitary deficiency. In adult nulliparous females panhypopituitarism is very rare. Anorexia nervosa is common in younger women. A diagnosis of anorexia nervosa should be made on positive psychiatric evidence and not by exclusion. Unfortunately, certain patients with panhypopituitarism may have major emotional and psychologic difficulties, in some instances due to a brain tumor and in other instances due to associated hypoglycemia. The most helpful single differential diagnostic test, however, is the response of the circulating eosinophils to epinephrine. A fall of 50 per cent or more eliminates generalized hypopituitarism. A negative test is of no aid in differential diagnosis. A very low initial eosinophil count (less than 50 cells per cu. mm.) is sufficient to eliminate severe anterior pituitary deficiency as a serious consideration, and is quite characteristic of severe anxiety states.

**Treatment.** Multiple pituitary trophic hormone therapy would be the agent of choice. Unfortunately, this is not available, and if it were, it is doubtful whether it could be used successfully as substitutive therapy for any prolonged period because of the tendency to form antibodies to this type of hormone preparation. In general the physician must rely on a nutritious diet with frequent small feedings and supplementary calcium, iron, and iodine; small doses of thyroid (U.S.P.) (100 mg. daily is usually a maximal dose, and should be attained slowly over a period of several months, beginning with 15 mg. daily); diethylstilbestrol, 0.5 mg., and methyltestosterone, 10 to 20 mg. daily in females (in males it may be desirable to give a slightly greater dose of methyltestosterone—i.e., 10 mg. three times a day); 5 ml. of aqueous adrenal extract, 1 ml. of "Lipo Adrenal Cortex," or 10 mg. of cortisone twice daily. One pellet (125 mg.) of desoxycorticosterone acetate may be implanted subcutaneously.

Cases with panhypopituitarism do poorly when they are submitted to surgical operations because of the lack of normal secretion of adrenocorticotrophic hormone. In these cases, the pre-operative administration of ACTH is definitely indicated. The hormone is given in doses of 10 to 25 mg. every six hours for five days before operation or until evidence of increased adrenal secretion has been obtained (e.g., fall of circulating eosinophils to very low levels, and increase in urinary excretion of 17-ketosteroids and 11-oxysteroids). Administration of the hormone is continued during the postoperative period until the patient has recovered from the acute effects of the operation.

#### HYPERFUNCTION

The existence of true panhyperpituitarism with hyperfunction of all known activities of the anterior pituitary has never been demonstrated. It is not uncommon, however, to note in patients with acromegaly or Cushing's disease associated hyperthyroidism, hypergonadism, gynecomastia, persistent lactation, or diabetes mellitus, presumably due to excess secretion of one or more of the other trophic hormones.

#### DISTURBANCES IN GROWTH HORMONE SECRETION

Only recently has it become possible to study the effect of purified preparations of growth

hormone. The studies of Li and Evans indicate that this hormone is a protein molecule of approximately 46,000 molecular weight with a powerful anabolic action (see table 50). Its action in experimental animals is characterized by a lowering of blood nonprotein nitrogen and amino acid levels and a decrease in urinary excretion of nitrogen. It also causes a rise in serum phosphorus and phosphatase with an increase in both the quantity and the rate of turnover of ribonucleic acid in the tissues. Its site of elaboration appears to be the acidophil cells of the hypophysis.

### HYPOFUNCTION

(See Lorain-Levi Syndrome, p. 551.)

**Prepubertal.** Prepubertal deficiency in growth hormone alone leading to dwarfism without associated sexual infantilism is not recognized. Most dwarfs with normal sexual and psychic development represent cases of primordial dwarfism or pygmyism.

**Postpubertal.** (See Simmonds' Disease p. 552.) At present there is no recognized syndrome representing pure growth hormone deficiency in the adult. With purified, potent growth hormone available for experimental study, it may become possible to establish definitely what effect, if any, growth hormone exerts on the normal metabolism of adult men and women. It has been suggested that osteoporosis, menopausal and senile, may reflect in part a deficiency of this hormone.

### HYPERFUNCTION

The clinical picture of growth hormone excess is modified by the age of onset. Thus, if the epiphyses have closed prior to the onset of the disorder, further growth of the long bones cannot occur, and the patient presents the highly characteristic stigmas of acromegaly. If, however, the onset occurs in childhood, gigantism overshadows the other manifestations. Finally, if the onset takes place during early adolescence, there may result a mixed type termed "acromegalic gigantism."

**Prepubertal—Gigantism:** PATHOLOGY. The underlying lesion is an eosinophilic or mixed-cell adenoma of the anterior lobe which may measure 2 to 5 cm. in diameter. There results excessive and proportional growth of all the organs. Relatively little is known of the pathologic anatomy in this condition.

**INCIDENCE.** It is not possible to collect accurate data on the incidence of gigantism because of its extreme rarity. Cushing has pointed out that adenomas of any sort are exceedingly rare in childhood and that one would not expect, therefore, the frequent occurrence of gigantism.

**CLINICAL PICTURE.** There is generalized symmetric overgrowth of the skeleton and soft tissues so that a well-proportioned giant is the result. At the onset, these individuals are usually physically strong, alert, and intelligent, with normal or increased libido and potency. Later in the disease, however, pituitary insufficiency may develop, and one then observes a person gigantic in skeletal stature but complaining of weakness and fatigability.

**DIAGNOSIS AND TREATMENT.** See under Acromegaly, below.

**Postpubertal—Acromegaly: PATHOLOGY.** An eosinophilic or mixed-cell adenoma of the hypophysis is invariably present. Rarely, the lesion may present carcinomatous changes.

There is generalized visceromegaly. The weight of the lungs is frequently more than twice normal; there is cardiac hypertrophy, the largest heart on record in this disease having weighed 1275 Gm.; the liver and kidneys are greatly enlarged. Persistence of the thymus is common. The brain appears to be the only exception to the general visceral hypertrophy.

The endocrine glands show variable changes. In approximately 50 per cent of the cases, the thyroid is enlarged. The most frequent histologic change appears to be the formation of adenomas in colloid thyroid tissue, although a few cases show parenchymatous thyroid hyperplasia. The adrenals are enlarged, but it is not entirely clear whether this is due to the generalized visceromegaly rather than to hyperplasia secondary to excess ACTH. The islets of Langerhans are frequently hypertrophied, and several cases have been reported with the finding of pancreatic adenomas. It is interesting to speculate what relation this may have had to the increase in islet cell function secondary to the diabetogenic action of the pituitary. The gonads show variable changes; most frequently they show histologic evidence of hypofunction rather than hyperfunction.

**INCIDENCE.** Acromegaly is a rare disease, occurring in approximately 1 in every 15,000 hospital admissions. About one half of all cases

appear during the third decade of life. There is no striking difference in sex incidence.

**CLINICAL PICTURE.** The presence of acromegaly may first attract a patient's attention because of increased size of head, hands, and feet, necessitating increased hat, glove, and shoe size; in other cases symptoms such as fatigue, apathy, headache, and muscle pain may constitute the presenting picture. The patients are frequently irritable and uncooperative, possibly due to the psychic repercussion of their unusual appearance or to the disease itself. The fully developed syndrome is unmistakable. The hands and feet are greatly enlarged. The digits have a square-shaped appearance. There is prognathism which may be so marked as to interfere seriously with mastication. The features are coarse, in part due to thickening of the skin; the malar and supraorbital ridges are prominent; the tongue is much enlarged and the lips are thickened (fig. 98). The speech is thick and hoarse.

Sexual activity may be increased at the outset, but is lost subsequently, and gonadal atrophy usually occurs. The appetite is voracious, and there may be polydipsia and polyuria. There is splanchnomegaly and enlargement of the heart. Cardiac failure is a not uncommon complication. In addition, the tumor often gives rise to pressure symptoms; approximately one half of the patients develop visual disturbances, and the majority have intractable headaches.

The course of the illness may be one of benign chronicity, in one instance lasting 50 years. A fatal termination is usually the result of hypopituitarism incident to cystic degeneration of the adenoma or following x-ray treatment. In such cases profound weakness and cachexia develop, and the patient succumbs rapidly to an intercurrent infection. Such a termination is the rule in gigantism and commonly occurs within a few years.

**DIAGNOSIS.** The diagnosis of the fully developed disease offers no difficulties. Visual field studies, roentgenograms, and metabolic studies afford important confirmatory data in early cases. There may be a variety of defects in visual fields resulting from pressure on the optic chiasma. Roentgenograms of the skull always show expansion of the sella turcica by a tumor which may attain the size of an apple. The flat bones, especially the calvarium, may be greatly thickened, and the vertebrae may show enlarge-

ment, particularly in the lateral projection. The extremities, in addition to being greatly enlarged, show characteristic tufting of the terminal phalanges (fig. 99).

Among the more important associated metabolic disturbances are enlargement of the thyroid

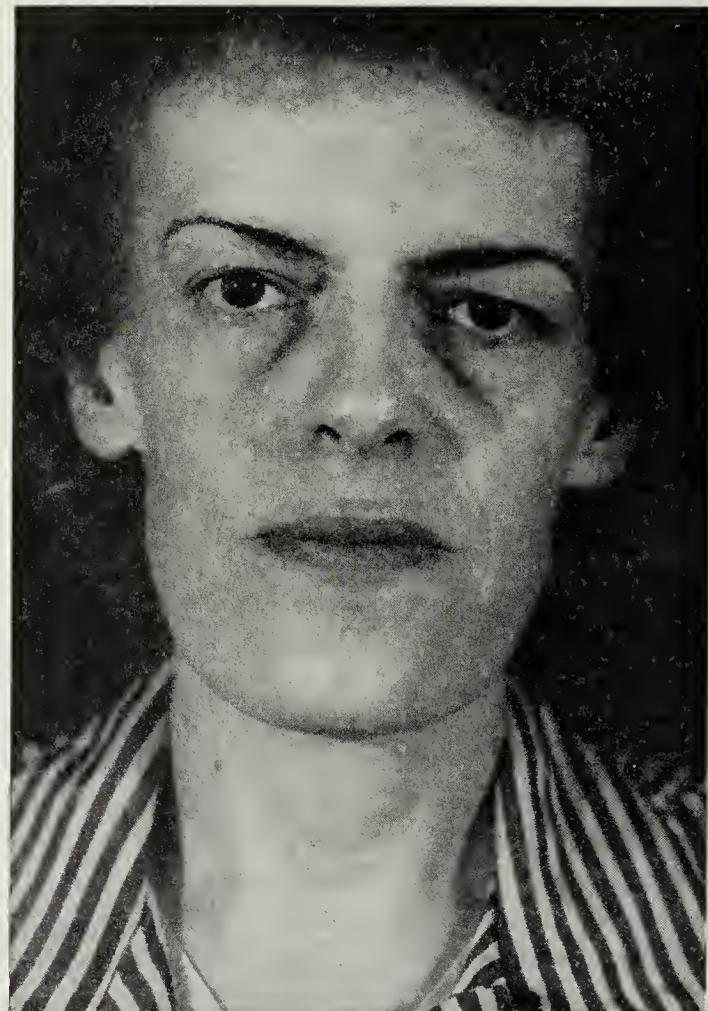


FIG. 98. Photograph of a 44-year-old woman with acromegaly, arrested. Onset of the disease occurred 20 years before, at which time a moderately enlarged sella turcica was demonstrated by x-ray. Following x-ray therapy of the pituitary she has shown no further progression of the disease.

with increased basal metabolic rate, and diabetes mellitus in approximately 10 to 15 per cent of cases. It is typically mild but insulin-resistant, often disappearing spontaneously.

A high level of serum inorganic phosphorus has been found to be characteristic of the active disease. It is probably due to growth hormone excess and usually falls to normal levels following surgical removal of the adenoma or successful treatment with x-ray or with testosterone and estrogenic hormones.

Hypopituitarism appears frequently later in the disease, either spontaneously or following

x-ray treatment. Since the bone changes are irreversible, the patient will continue to present his peculiar appearance. On the other hand, weakness and fatigue with a lowered basal metabolic rate, hypotension, and hypoglycemia will

procedure. Following x-ray treatment it may be necessary to provide substitution hormone therapy in the form of thyroid and gonadal and adrenal hormones (see under Panhypopituitarism, p. 554).

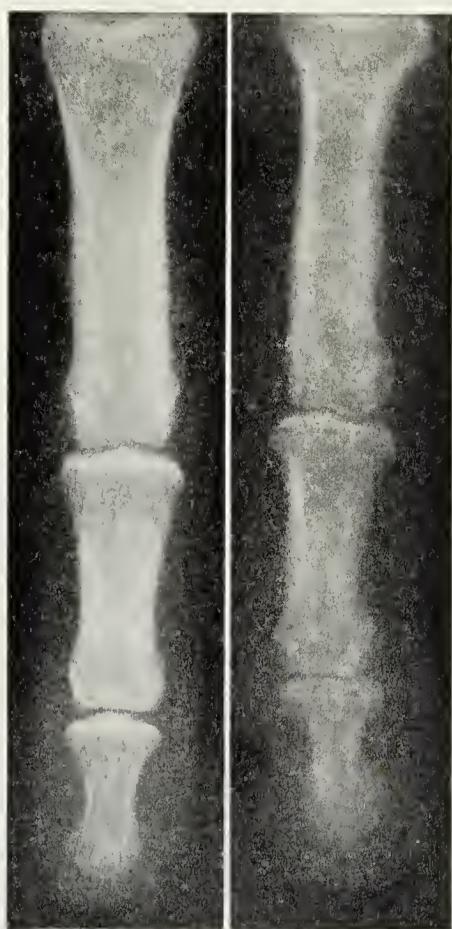


FIG. 99. Characteristic tufting or "arrowhead" appearance of the terminal phalanx in acromegaly (right). Normal phalanx for comparison (left). Note also the thickness of the acromegalic finger.

indicate a hypopituitary rather than a hyperpituitary state.

**TREATMENT.** Although eosinophilic adenomas of the pituitary appear to be the most amenable of all hypophyseal tumors to surgery, the spontaneous remissions which the disease often manifests and the radiosensitivity of the eosinophil cells render irradiation the treatment of choice unless progressive involvement of vision occurs. Doses of from 25 to 50 mg. of testosterone propionate daily in the male, and the equivalent of from 0.05 to 0.3 mg. of ethynodiol diacetate daily in the female, are efficient in relieving some of the symptoms and in reducing the serum inorganic phosphorus. Such treatment should be used, however, only as a temporary palliative

### DISTURBANCES IN ADRENOCORTICOTROPHIN SECRETION

In 1916 P. E. Smith demonstrated underdevelopment of the adrenal cortex of the frog following removal of the hypophyseal anlage. Later Evans, Houssay, and Smith himself produced the same effect in other species, and they were also able to prevent this underdevelopment by the administration of anterior pituitary implants or extracts. These experiments led to the postulation of an adrenocorticotropic hormone (ACTH). In 1943 the hormone was purified, crystallized, and characterized by Li and Sayers simultaneously (see table 50). This hormone appears to stimulate all known functions of the adrenal cortex. It leads to the formation of desoxycorticosterone-like substances, which result in sodium retention and potassium excretion. The injection of ACTH also produces an increased 11-oxysteroid secretion, resulting chiefly in increased liver glycogen formation, a rise in blood sugar and uric acid excretion, and a fall in circulating eosinophils and lymphocytes. Finally, adrenal androgens appear to be increased, as manifested by an increased urinary 17-ketosteroid excretion. The metabolic action of ACTH is not so constant or predictable as that of the pure adrenal steroids, since its effect is dependent upon adrenal cortical function, a highly variable factor. Furthermore, the same pure adrenal hormone may produce quantitatively and even qualitatively different changes with respect to a given metabolite; depending, for example, upon the body stores of that particular metabolite, or the general state of nutrition of the individual. Whether the adrenal secretes one type of steroid which later becomes transformed into three or more hormones, or whether compounds of the "salt-retaining," "glucogenic," and "androgenic" varieties are secreted separately by the adrenal cortex has not been elucidated.

The assay of ACTH is dependent upon the ability of the hormone to deplete the content of ascorbic acid or cholesterol of the hypophysectomized rat adrenal.

Control of ACTH secretion by the pituitary is thought to be dependent chiefly upon the level of circulating adrenal hormones. Under circumstances of acute stress, epinephrine may be responsible for liberating ACTH from the pituitary.

The administration of ACTH in doses of 10 to 25 mg. for short periods of time produces very few toxic symptoms. The prolonged administration of ACTH, for periods of weeks or months, may lead to the appearance of a "Cushing-like" clinical state, with lowering of the serum chloride and potassium, leading to clinical symptoms of hypokalemia, a rise in carbon dioxide-combining power, diabetes mellitus, and virilism.

In contrast to other protein hormones from the anterior pituitary, ACTH appears to have very slight antigenic properties. Experiments suggest that this low antigenicity results, not so much from the nature of the molecule, the active portion of which is a polypeptide, as from the fact that ACTH stimulates a large output of adrenal steroids which in themselves, by some unknown mechanism, reduce the formation of antibodies.

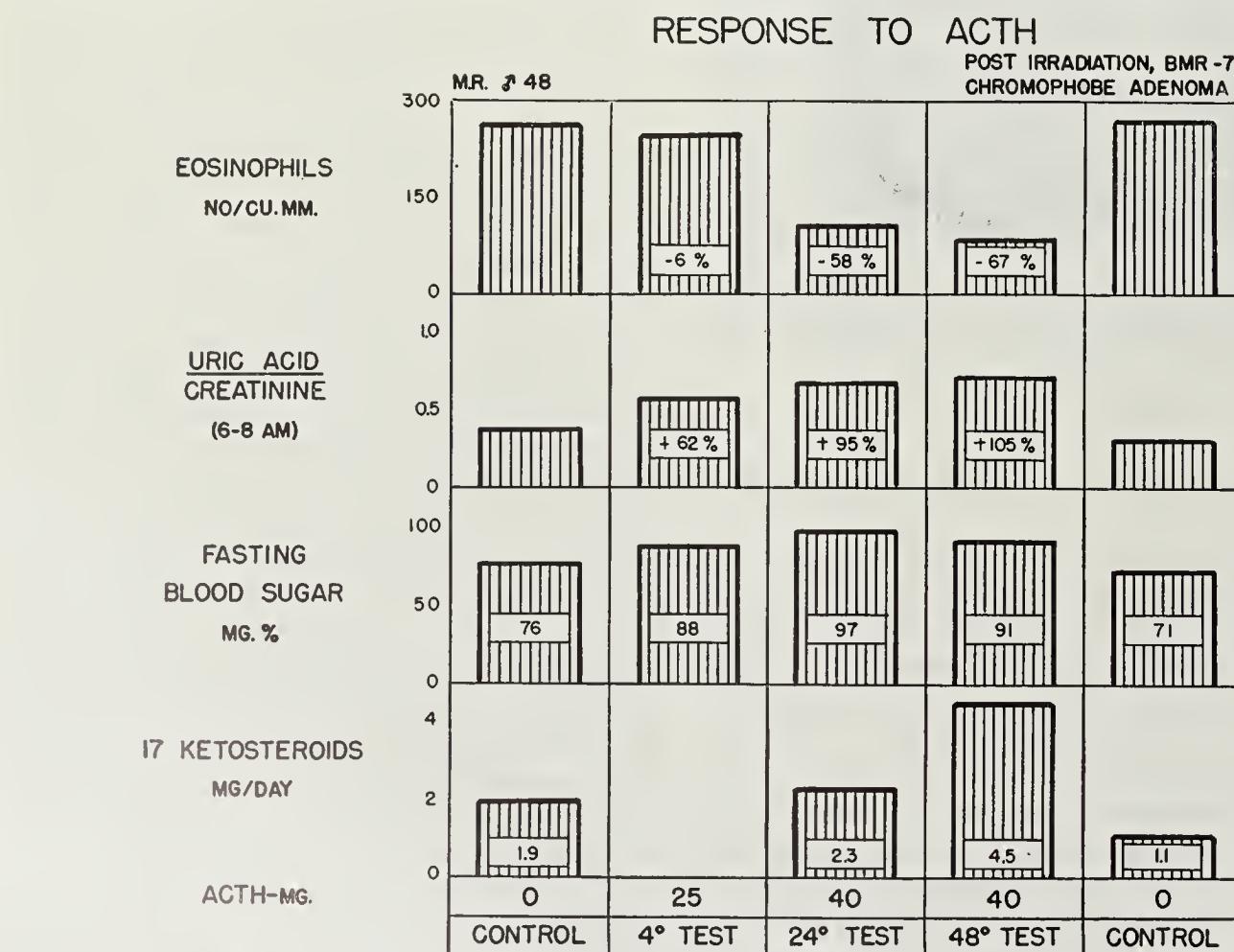


FIG. 100. Response of a patient with secondary adrenal insufficiency to ACTH. A single dose failed to provoke significant changes. Following the administration of ACTH for 48 hours, there was evidence of marked adrenal stimulation.

### HYPOFUNCTION— “PITUITARY-ADRENAL CORTICAL DEFICIENCY”

Deficiency of adrenocorticotrophic hormone is almost invariably associated with other anterior pituitary hormone deficiencies. It may so dominate the clinical picture, however, that it becomes difficult to distinguish it from primary adrenal cortical insufficiency. In adrenal insufficiency secondary to pituitary failure there is usually *minimal pigmentation*, together with signs of associated thyroid and gonadal deficiency.

It is usually possible to distinguish cases of Addison's disease from cases of adrenocorticotrophic insufficiency by the patient's response to prolonged ACTH administration. In contrast to normal people, neither "Addisonians" nor patients with hypopituitarism respond to a single 25 mg. injection of ACTH. If ACTH is given for 48 hours, however, in doses of 10 mg. every six hours, "Addisonians" do not respond significantly, whereas cases of secondary adrenal cor-

tical insufficiency show a fall in the levels of circulating eosinophils, a rise in the uric acid/creatinine ratio, and a rise in the urinary excretion of 17-ketosteroids (fig. 100) (see 48-Hour ACTH Test, Chapter 57, p. 595). These changes do not take place, however, if the adrenocorticotrophic insufficiency has been severe enough to produce irreversible adrenal cortical atrophy. This, however, is rare. An occasional case of secondary hypoadrenocorticism will require more than 48 hours of ACTH administration for evidence of activation.

**Treatment.** It may be possible to stimulate the adrenals by administering repeated short courses of ACTH, since an antigenic response is not readily induced by this hormone. In general, however, one must depend upon substitution therapy with adrenal cortical hormone preparations. The quantity of desoxycorticosterone required by such patients is usually very small and may be met by giving 1 mg of desoxycorticosterone acetate in oil, intramuscularly, once daily, or by implanting subcutaneously one pellet (125 mg.). (See Addison's Disease, Treatment,

p. 598). To attain maximum improvement, whole adrenal extract or cortisone is necessary. Five to 10 ml. of aqueous adrenal extract, or 1 to 2 ml. of "Lipo Adrenal Cortex," or, if available, 5 to 10 mg. of cortisone twice daily is an adequate dose. Associated thyroid and gonadal deficiency should be treated. Thyroid extract should be administered with precaution and always in conjunction with whole adrenal extract or cortisone (see Addison's Disease, Treatment, p. 597). *Preoperative treatment with ACTH is imperative in these patients* (see Panhypopituitarism, Treatment, p. 554).

## HYPERFUNCTION

(See Cushing's Syndrome, Chapter 57,  
p. 599.)

It has become apparent that the clinical syndrome described by Cushing may be due either to excessive secretion of pituitary adrenocorticotrophin (Cushing's disease or "pituitary basophilism") or to primary hypersecretion of the adrenal cortex from tumor or hyperplasia (Cush-



FIG. 101. Photographs of a 38-year-old woman with Cushing's disease. (1) Patient before the onset of the disease, age 33. (2) Patient five to six months after the onset of symptoms, age 37. (3) Improvement following x-ray treatment to the pituitary (2800 roentgen units) and to the adrenal regions (600 roentgen units). (4) Return of the full-blown disease, just prior to admission to the Peter Bent Brigham Hospital.

ing's syndrome). Rarely, certain ovarian tumors may give an identical picture. It is possible that in some cases of Cushing's syndrome, particularly those due to bilateral adrenal hyperplasia, the disease may have been initiated by excess of ACTH, with subsequent development of an independent adrenal cortical hyperfunction.

The clinical characteristics have been detailed elsewhere (see Cushing's Syndrome, Chapter 57, p. 599). From a diagnostic standpoint, the most important changes are obesity, hirsutism, round face, purple abdominal striae, hypertension, diabetes, elevated erythrocyte count, osteoporosis, moderately elevated 17-ketosteroid excretion, markedly elevated 11-oxysteroid excretion, high initial uric acid/creatinine ratio (above 0.8), and low circulating eosinophil levels (below 30 per cu. mm.), together with polymorphonuclear leukocytosis and lymphopenia.

In early cases of true Cushing's disease (ACTH excess), irradiation of the pituitary with doses of 3000 to 4500 roentgen units may result in marked clinical improvement (fig. 101). In cases of Cushing's syndrome, irradiation therapy also may prove beneficial, but, as a rule, removal of adrenal tissue is necessary to cure the syndrome (see Cushing's Syndrome, Chapter 57, p. 601).

### DISTURBANCES IN THYROTROPHIN SECRETION

Ascoli and Legnani, in 1911, were the first to demonstrate the atrophy and inactivity of the thyroid which follows hypophysectomy in the mammal. Later studies by Allen and by P. E. Smith revealed that transplants or extracts of the anterior hypophysis prevented this atrophy. Loeb and Burnett prepared the first crude thyroid-stimulating extracts in 1929. Methods for the preparation of thyrotrophic hormone have been improved considerably, but the hormone has not as yet been completely purified. No simple satisfactory method for the assay of TSH has been devised.

Injection of TSH results in discharge of the stored thyroid hormone from the gland, with a subsequent increase in height of the thyroid epithelium. The uptake of iodine by the gland is increased (see p. 569). TSH secretion is thought to be dependent upon the level of circulating thyroid hormone. It is probable that hypothalamic stimuli may also control the production and release of this hormone.

### HYPOFUNCTION— “PITUITARY MYXEDEMA”

(See Panhypopituitarism, p. 551.)

Hyposecretion of thyrotrophin alone has not been recognized clinically. As is the case with deficiency in ACTH secretion, TSH decrease is usually accompanied by deficiency of one or more of the other anterior pituitary hormones.

There are occasional cases of pituitary disease in which the appearance of myxedema so colors the clinical picture that the differential diagnosis from primary thyroid myxedema is exceedingly difficult. The differential diagnosis is particularly important, as thyroid medication in patients with pituitary deficiency may precipitate an adrenal crisis due to the secondary adrenal cortical insufficiency which is almost always present. A history of amenorrhea in the female, particularly following childbirth or when unaccompanied by hot flushes; the finding of atrophy of the breasts, vagina, and uterus with scant axillary and pubic hair in the female; loss of potency and libido in the male; and marked persistent hypotension all suggest that the case is one of secondary rather than of primary myxedema. The serum cholesterol is frequently found to be normal or low; there is marked insulin sensitivity, a low FSH urinary excretion, and very low levels of urinary 17-ketosteroid excretion.

Treatment is essentially similar to that of Simmonds' disease (see Panhypopituitarism, p. 554).

### HYPERFUNCTION

(See Exophthalmic Goiter, Chapter 55, p. 573.)

It is an attractive hypothesis to assume that thyrotoxicosis is frequently caused by a primary increase in pituitary TSH secretion. TSH secretion may be increased by stimuli arising in the hypothalamus, and it is thought that such a mechanism may be an explanation of the sudden appearance of thyrotoxic symptoms following major emotional or psychic trauma. There is no doubt that an increase in TSH secretion must be involved in certain cases of Graves's disease or exophthalmic goiter and most certainly operates in patients with acromegaly or Cushing's disease with associated hyperthyroidism. It is impossible at present to know with certainty the frequency with which this mechanism is responsible for

initiating the thyroid hyperplasia. The ability to demonstrate with relative ease normal or increased TSH secretion would clarify this situation. It is possible that certain cases of hyperthyroidism may be initiated by an excess of TSH with subsequent development of independent thyroid overactivity.

Thyrotoxicosis, regardless of origin, is controlled successfully in most cases by reducing the activity of functioning thyroid tissue by subtotal thyroidectomy, thiouracil therapy, or radio-iodine treatment. A clearer understanding of the etiologic relationships, however, might modify treatment significantly, depending upon whether the disease originated primarily in the gland or was extrathyroid in origin (see Chapter 55, p. 573).

### DISTURBANCES IN GONADOTROPHIN SECRETION

Three gonadotrophic hormones have been identified: (1) follicle-stimulating hormone (FSH, thylakentrin), which is necessary for maturation of the follicle and estrogen formation in the female and for maintenance of normal spermatogenesis in the male; (2) luteinizing hormone (LH, interstitial cell-stimulating hormone, ICSH, metakentrin), which is also necessary, in conjunction with FSH, for estrogen production from the follicle, and leads to ovulation and formation of the corpus luteum in the female; in the male, it maintains normal interstitial cell function; (3) luteotropic hormone (LTH, luteotrophin, lactogenic hormone), which is necessary for maintenance of the corpus luteum. In addition, LTH leads to formation of milk from mammary ducts previously stimulated by estrogens (see Chapter 62).

Large doses of sex hormones depress the secretion of gonadotrophins by the pituitary. Conversely, release of gonadotrophins is increased after castration. It is generally thought, therefore, that the level of circulating estrogens or androgens regulates the production of gonadotrophins by the hypophysis. Recently, evidence has been brought forward suggesting that inactivation of the gonadotrophins by the normal ovary may well be an important mechanism in this regulation.

FSH excretion is estimated in the human by injecting varying dilutions of urine dialysates or ultrafiltrates into immature female mice. A posi-

tive response is gauged by the increase in weight of the mouse uterus; the results are expressed in mouse units of FSH excreted in 24 hours, one mouse unit (m.u.) being defined as that quantity of FSH which is sufficient to stimulate the growth of one mouse uterus. Values below 6 m.u. per 24 hours are considered abnormally low. The excretion may rise considerably in the presence of gonadal failure. There are no practical ways of assaying the excretion of LH and LTH.

Since the various gonadotrophins have markedly different effects in both sexes, it will be necessary to discuss the effects of lack or excess of these hormones in the male and female separately.

In most cases, there exists a deficiency of all three gonadotrophins, with insufficiency of other trophic hormones as well (see Panhypopituitarism, p. 552). The existence of insufficiency of a single gonadotrophin is a matter of speculation, but in certain disorders the clinical picture is characteristic enough to suggest that one type of gonadotrophin is chiefly involved.

#### FEMALE

**Follicle-Stimulating Hormone: Insufficiency.** If the failure of FSH secretion takes place in the *prepubertal* period, there results lack of sexual development at the time of puberty. *Postpubertal* FSH failure is followed by involution of the Graafian follicles and diminution of secondary sex characteristics. The vagina, uterus, and breast atrophy as a result of estrogen lack. There is diminished excretion of FSH in the urine. Of first importance is the detection and therapy of a specific cause, such as tumor of the hypophysis or hypothalamus. Supplementary gonadotrophin therapy is limited to diagnostic differentiation between primary and secondary ovarian failure. In most instances ovarian substitution therapy is necessary—i.e., 0.1 to 0.5 mg. of diethylstilbestrol.

**HYPERFUNCTION—METROPATHIA HEMORRHAGICA.** It is thought that excess FSH in relation to LH secretion may cause the “hyperfolliculoidism” of metropathia hemorrhagica (see Metrorrhagia, Chapter 62, p. 642).

**Luteinizing Hormone (LH, ICSH): Insufficiency—METROPATHIA HEMORRHAGICA.** A relative lack of LH may be the underlying cause of the persistent action of the Graafian follicle in metropathia hemorrhagica (see Metrorrhagia,

Chapter 62, p. 642). A lack of LH might also lead to a failure to ovulate and therefore produce sterility in the female (see Infertility, Chapter 63, p. 643).

**HYPERFUNCTION—PERSISTENT CORPUS LUTEUM.** Certain cases of hyperluteinism, having as their base persistent corpora lutea or corpus luteum cysts, may reflect a disturbance in gonadotrophin secretion, with excess LH. Some of these cases give a picture similar to that of ectopic pregnancy, with delayed menstruation, pain in one or the other lower abdominal quadrant, and a small, tender mass in the corresponding side of the pelvis. Progestational transformation of the endometrium, enlargement of the breast, and secretion of colostrum are frequently present. In differentiating ectopic pregnancy from persistent corpus luteum, some aid may be derived from the fact that the "pregnancy test" is positive with much greater frequency in ectopic pregnancy.

**Luteotropic Hormone (LTH) : INSUFFICIENCY—(?) THREATENED ABORTION.** Progesterone is of great importance for the nidation and fixation of the ovum and for the maintenance of early pregnancy. Many cases of threatened abortion appear to be due to an insufficiency of progesterone; hence the possibility that this condition might be due to a deficiency of LTH. Progesterone in doses of 15 to 25 mg. three times a day may be beneficial in some cases.

**HYPERFUNCTION—(?) GALACTORRHEA.** It is possible that an excess of LTH may cause hypersecretion of milk. Such a mechanism may be operating in certain cases of acromegaly with galactorrhea. Treatment is that of the underlying cause.

#### MALE

**Follicle-Stimulating Hormone (FSH) : INSUFFICIENCY—OLIGOSPERMIA.** FSH insufficiency in the male would produce a deficient maturation of spermatozooids, with resulting oligospermia and sterility. This is a frequent finding in panhypopituitarism; that such a mechanism operates without associated pituitary trophic deficiency has never been proved.

**HYPERFUNCTION.** No syndrome can be attributed directly to an excessive FSH secretion in the male. Abnormally high urinary values of FSH are found in castrates.

A syndrome characterized by gynecomastia,

aspermatogenesis, and increased FSH excretion with normal Leydig cells has been described (Klinefelter syndrome—see Testes, Chapter 61, p. 634). That the increased FSH is probably secondary to the destruction of the testicular Sertoli cells is suggested by the cases reported by de Castillo and his group showing normal Sertoli cells and FSH excretion.

**Interstitial Cell-Stimulating Hormone (Luteinizing Hormone, LH, ICSH) : HYPOFUNCTION.** Hypoleydigism and decreased gonadal androgens would theoretically result from LH insufficiency in the male. There results a picture of eunuchoidism (see Testes, Chapter 61, p. 631). Froehlich's syndrome and the Laurence-Moon-Biedl syndrome are associated with failure of gonadal development.<sup>2</sup> Since no constant lesions are observed in the anterior pituitary, it is assumed that the syndromes arise from deranged gonadotrophin secretion secondary to hypothalamic disturbances. In certain instances the Froehlich syndrome is associated with intrasellar or suprasellar tumor. A few of the cases of Laurence-Moon-Biedl syndrome have shown an excess of basophils in the pituitary. The clinical picture in Froehlich's syndrome is a combination of adiposity and genital atrophy. The two cardinal manifestations may make their appearance at different times. There is underdevelopment of the gonads and secondary sex characteristics and a white, delicate skin. Depending upon the etiologic factor (tumor), one may observe mental retardation, visual disturbances, diabetes insipidus, and disturbances in skeletal growth. It is important to differentiate between cases of *Froehlich's type of habitus* (obesity, genu valgum, and flat feet) and true Froehlich's syndrome. The former actually have normal sex organs which may be hidden in the adipose tissue. Restoration of weight to normal is usually sufficient to correct the condition. Many such boys at the time of puberty develop normally without any treatment. In Froehlich's syndrome associated with tumor, the treatment indicated is removal of the tumor if possible, particularly if there is any evidence of pressure on the optic chiasma. Otherwise, pituitary gonadotrophin may be used as a diagnostic-therapeutic test, to be followed by testosterone in males and estrogenic hormone in

<sup>2</sup> The Laurence-Moon-Biedl syndrome also occurs in the female. It is discussed here for the sake of convenience.

females. In addition, it is important to control body weight.

The Laurence-Moon-Biedl syndrome is a hereditary disease characterized by adiposity, genital dystrophy, mental retardation, skull deformities, and associated congenital malformations such as polydactyly and retinitis pigmentosa. Less than 100 cases have been reported, and pathologic data have failed to reveal the underlying cause. There is no radiologic evidence of pituitary lesions in these patients. The adiposity and genital dystrophy are assumed to be caused by a congenital malformation in the hypothalamic region. No effective therapy is known.

**HYPERFUNCTION.** This would result in hyperleydigism and increased virilism. This mechanism might conceivably explain the increased libido and potency which occurs early in the course of acromegaly and gigantism.

**Luteotrophic Hormone (LTH): HYPOFUNCTION.** There is no syndrome referable to lack of LTH secretion in the male.

**HYPERFUNCTION.** Excess of LTH might explain the galactorrhea which rarely occurs in the male.

### TUMORS OF THE PITUITARY

Pituitary adenomas, often microscopic in size, are found in approximately 10 per cent of human pituitary glands. They may be classified upon the predominance of cell type into chromophobe, eosinophilic, and basophilic adenomas. Eosinophilic adenomas are usually limited in location to the anterior pituitary, whereas basophilic adenomas not infrequently are located within the pars nervosa. A rare type of tumor is the so-called adenoma psammosum, the cells of which are poor in cytoplasm and surround hyalinized or calcified concretions.

Other types of pituitary tumors include carcinomas, cysts lined with ciliated epithelium, and craniopharyngiomas.

Pituitary adenomas of the eosinophilic or basophilic type may be accompanied by excessive hormone secretion (see Acromegaly (p. 555) and Cushing's Syndrome, Chapter 57). In all types of tumors of the pituitary, decreased function is likely to occur late in the disease as a result of increased pressure and necrosis. In tumors treated by x-ray there is likely to be a general reduction in pituitary function on the basis of irradiation effect alone, independent of the mechanical effect of the tumor itself. Because of

the proximity of the optic chiasma and hypothalamic region, signs and symptoms of disturbance in vision and vegetative functions are common as tumors or cysts increase in size (see Panhypopituitarism, p. 551).

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# 54

## Diseases of the Posterior Pituitary Gland

George W. Thorn and Peter H. Forsham

Nature of Posterior Lobe Hormone  
 Deficiency of Posterior Lobe Hormone  
 Diabetes Insipidus  
 Excess of Posterior Lobe Hormone  
 Oxytocic ("Pitocin") Factor  
 Melanophore-Dispersing Hormone (Intermedin)  
 Introduction  
 Chemical Characteristics  
 Clinical Studies  
 Summary

### NATURE OF POSTERIOR LOBE HORMONE

From the posterior lobe of the hypophysis—and to a lesser extent from its stalk and the tuber cinereum—extracts can be prepared which, when injected into animals, have a number of characteristic effects. Principally, they enhance the reabsorption of water by the renal tubules (antidiuretic effect); stimulate the smooth muscle of the intestine; stimulate uterine contraction (oxytocic effect); and cause constriction of arterioles and capillaries and, in anesthetized animals only, a rise in blood pressure (vasopressor effect). With regard to the latter action, it is perhaps not generally appreciated, although of obvious practical significance, that posterior lobe preparations as used therapeutically in man have no consistent effect on blood pressure, probably because of compensatory adjustments elsewhere in the circulation.

Since the chemical structure of the compound or compounds responsible for these physiologic effects is far from established, preparations must

be assayed in terms of biologic activity. Assay may conveniently be carried out with reference either to oxytocic or to vasopressor activity, and, in principle, consists of the comparison of the activity of an unknown preparation with that of an international standard posterior pituitary powder. One International U.S.P. or B.P. Unit of oxytocic or of vasopressor activity is defined as the activity of 0.5 mg. of the reference standard. In crude extracts of the posterior lobe, the biologic activity appears to reside in a homogeneous protein or polypeptide fraction having a molecular weight of the order of 30,000 and an isoelectric point of 4.8; such fractions show approximately equal vasopressor and oxytocic activities in terms of the reference powder, of the order of 16.6 I.U./mg. From the breakdown of such fractions it has been possible to obtain polypeptides of molecular weight of 600 to 2000 which, milligram for milligram, display many times the pressor (450 I.U./mg.) and oxytocic (700 I.U./mg.) activities of the mother fraction. Of more immediate clinical importance has been the demonstration that crude posterior pituitary extract can be separated into two physiologically distinct fractions: the first, *oxytocin* (trade-mark, "Pitocin"), is highly potent in oxytocic activity with only traces of vasopressor and antidiuretic activity; the second, *vasopressin* (trade-mark, "Pitressin"), shows marked antidiuretic and pressor potency with a trace of oxytocic activ-

ity. It has never been possible to separate significantly the antidiuretic and pressor effects. Whether these fractions exist as distinct chemical entities in the crude extracts, or are formed by the splitting of some larger molecule, remains a matter of speculation.

The antidiuretic effect of posterior pituitary extract deserves further comment. Besides stimulating the tubular reabsorption of water, it has been shown to inhibit the reabsorption of chloride and sodium (chloruretic and natriuretic actions) and to stimulate the reabsorption of phosphate. The chloruretic and natriuretic actions have been shown to be properties of the oxytocin fraction which is also present as a contaminant in vasopressin. Oxytocin, interestingly enough, is actually diuretic in effect, although this action is often masked by the contaminating vasopressin. The activity of posterior lobe extracts on the renal tubules with respect to sodium, chloride, and water is directly opposed to that of desoxycorticosterone; and indeed, under appropriate experimental conditions, these two agents can be shown to neutralize each other's renal effects. The role of the neurohypophysis in Addison's disease thus becomes a matter of some theoretic importance, especially since the urine of patients with Addison's disease has been shown to contain a high titer of antidiuretic substance. Finally, it should be pointed out that the antidiuretic effect of posterior lobe extracts varies inversely with the osmotic pressure of the body fluids, appearing most prominently in animals given a liberal water load. In fact, in the dehydrated organism, even "Pitressin" exerts a *diuretic* effect, probably an osmotic diuresis secondary to the increased output of sodium and chloride.

Present evidence permits us to assign endocrine activity to the neurohypophysis only with respect to an antidiuretic hormone (ADH). None of the other activities of posterior lobe extracts have been shown to be of significance in the intact organism. It is well established that the neurohypophysis normally elaborates an antidiuretic hormone which, by stimulating the renal tubular reabsorption of water, is of profound significance in the regulation of the osmotic pressure of the body fluids. The adequate stimulus for its release is probably a rise in the osmotic pressure of the internal environment; nerve impulses are then thought to be set up in osmo-

receptors (located, recent evidence suggests, in the carotid arteries) and relayed through certain hypothalamic centers which have direct neuronal connections with the posterior lobe of the pituitary. It should be obvious from what has been said, that the antidiuretic hormone is a functional rather than a chemical entity, which cannot as yet be completely equated with any of the known extracts of its gland of origin.

## DEFICIENCY OF POSTERIOR LOBE HORMONE

### DIABETES INSIPIDUS

**Introduction.** Diabetes insipidus is a chronic symptom complex characterized by the passage of large quantities of pale, dilute urine, with secondary polydipsia. It results from some defect in the chain of events by which antidiuretic hormone (ADH) is released from the neurohypophysis and acts on the cells of the renal tubules. The classic anatomic and physiologic studies of Fisher, Ingram, and Ranson revealed that the disease may be caused by interference, at any level, with the functional integrity of the neurohormonal unit comprising the supraoptic and paraventricular nuclei of the hypothalamus, the posterior lobe of the hypophysis, and the intervening nerve tracts. It should be noted that complete hypophysectomy has never been known to produce diabetes insipidus, so that damage to the neurohormonal unit responsible for the elaboration of ADH does not, *per se*, produce the syndrome *unless* the anterior pituitary lobe remains functionally intact. By inference, then, the latter structure may be considered to give rise to one or more agents which, directly or indirectly, oppose the action of ADH. Water diuresis is thus seen to depend upon an end organ (the renal tubule) responding to ADH on the one hand, and, on the other, to certain diuretic agents as yet imperfectly characterized but probably including compounds elaborated by the adrenal cortex. And, while the majority of cases of diabetes insipidus are indubitably the result of a deficiency of ADH, one might anticipate, *a priori*, the existence of cases due either to unresponsiveness of the renal tubule or to increased amounts of diuretic substances; in either case, refractoriness to "Pitressin" might be expected to characterize the disease in contrast to those cases brought about by ADH deficiency. As a matter of fact, 5 to 15 per cent of

cases of diabetes insipidus are refractory to "Pitressin" to some degree. And in recent years there has appeared a small group of cases, mostly familial, in which considerable evidence suggests a hereditary refractoriness of the renal tubules as the primary defect.

**Incidence.** Diabetes insipidus is a rare disease, having a slightly greater incidence in youth and in males. Rowntree reported 10 and 16 cases respectively in two series of 100,000 patients admitted to the Mayo Clinic.

**Etiology.** As shown by Fink's pathologic studies in 107 cases, the great majority of instances of this disease are due to anatomic lesions involving the hypothalamic-hypophyseal system and hence, presumably, interfering with the production of ADH. In clinical practice, it will often be found impossible to elicit any other evidence of such a lesion; while the label "idiopathic" may be justifiable for such cases *ante mortem*, the finding of an anatomic lesion at autopsy generally may be predicted.

**Pathology.** The primary pathologic processes associated most frequently with the syndrome have been tumors of the diencephalopituitary region, basilar meningitis, and, in children, xanthochromatosis (Hand-Schüller-Christian syndrome). Transitory and occasionally permanent polyuria frequently follows severe cranial injuries. Pathologic changes consist of those due to the primary disorder, such as tumor, brain injury, inflammation, etc.; and secondary changes in the urogenital tract, such as dilatation and hypertrophy of the bladder with megaloureters.

**Clinical Picture.** The chief symptoms of diabetes insipidus are polyuria and polydipsia. The loss of large amounts of pale urine of low specific gravity (1.001 to 1.005), often as much as 15 to 20 liters per day, results in dehydration and, consequently, in such related symptoms and signs as dry skin, constipation, and an intense, almost insatiable thirst with corresponding polydipsia. Water deprivation to the limit of tolerance does *not* prevent polyuria, nor does it lead to a significant increase in urinary specific gravity. Thus, in this disease, polydipsia is secondary to polyuria, in contrast to patients with psychogenic polydipsia who pass large quantities of urine as an aftermath of a large fluid intake. In patients with diabetes insipidus, no consistent physical or chemical changes are noted other than those of dehydration. However, there may

be symptoms referable to the localized disease process causing the syndrome.

The role of trauma in the production of diabetes insipidus deserves special comment, since the polyuria which sometimes follows head injury is not infrequently transient as contrasted with the chronicity of most other forms of the disease. A similar syndrome may also develop after surgical operations, particularly intracranial surgery. Indeed, recent studies indicate that some degree of polyuria is almost the rule following major surgery. When the full-blown syndrome develops in this situation, it may rapidly induce serious dehydration. This dehydration, which is due principally to water loss, may be accentuated by the administration of isotonic rather than hypotonic saline solutions. This type of diabetes insipidus is usually refractory to "Pitressin" and is best treated by providing an adequate quantity of water or glucose solution without added saline.

**Diagnosis.** The symptoms plus the large urine volume with specific gravity below 1.008, unassociated with a history or other findings of diabetes mellitus or of chronic renal disease, will quickly suggest diabetes insipidus. Since, however, this diagnosis commits the patient to a regime of daily injections for an indefinite period, it is not to be made lightly, and the clinical impression should be supported by careful studies made under hospital conditions. All cases of diabetes insipidus, moreover, should be studied carefully for active intracranial lesions which should be presumed present until proved otherwise. Thus, examination should include, in addition to the differential tests of water excretion outlined below, a study of the spinal fluid, roentgenograms of the skull and chest (metastatic disease), electroencephalogram, serologic test (syphilis), and serum protein level and sternal marrow aspiration (multiple myeloma).

**Differential Diagnosis.** The syndrome must be differentiated from psychogenic polydipsia, chronic nephritis, and diabetes mellitus. Chronic nephritis may be excluded by the absence of protein or formed elements in the urine, a normal blood nonprotein nitrogen level, and normal kidney function tests. Often the most difficult differential diagnosis is that between diabetes insipidus and psychogenic polydipsia. Other tests which are helpful in differential diagnosis include:

1. Dehydration of the patient with inability to increase the specific gravity of the urine. Such

a response differentiates diabetes insipidus from psychogenic polydipsia but not from chronic nephritis. Great care must be taken in suspected "psychogenic" cases to be certain the patient does not have access to water or other fluids.

2. Alleviation of symptoms with repeated small doses of "Pitressin"—i.e., 0.2 ml. every three to four hours day and night. This differentiates diabetes insipidus from chronic nephritis, but not from psychogenic polydipsia, which is often ameliorated by "Pitressin." Moreover, the possibility of "Pitressin"-resistant diabetes insipidus must always be kept in mind.

3. Response to hypertonic saline infusion by increased diuresis and chloruresis. This test is perhaps one of the most conclusive in excluding psychogenic polydipsia.

**Technic.** After a preliminary eight-hour period of fluid restriction, the patient is hydrated with 20 ml. of water per kilogram of body weight over a one-hour period. An infusion of 3 per cent saline (10 ml. per kg.) is given over a 45-minute period. Urine is collected at 15-minute intervals, preferably by catheter, during the period of hydration, the infusion, and the half-hour control period following the infusion. The urine flow rate is determined; if the test is to be satisfactory, this should exceed 5 ml. per minute during the two 15-minute control periods which immediately

precede the infusion. In normal subjects there is a marked falling off of flow after the infusion of hypertonic saline has been started (see figure 102). In diabetes insipidus the urine flow does not decrease. It is only after the administration of 0.1 unit of "Pitressin" that an inhibition of the diuresis is detected. The value of the test lies in the fact that it differentiates psychogenic polydipsia from true diabetes insipidus and, by the response to "Pitressin," differentiates renal disease from true diabetes insipidus.

**Treatment.** Treatment of diabetes insipidus may be divided into two phases: (1) correction of the underlying intracranial difficulty, if present; and (2) replacement therapy with the anti-diuretic hormone.

Usually the hormone must be continued throughout life. It may be given as subcutaneous injection of "Pitressin," as nasal insufflation of powdered posterior pituitary, or preferably as "Pitressin Tannate in Oil" by subcutaneous or intramuscular injection.

"Pitressin" is a brand of vasopressin or beta-hypophamine; it is supplied in 0.5 and 1 ml. ampuls with a strength of 20 I.U. of pressor activity per ml. The quantity of "Pitressin" required to ameliorate the symptoms is very small, but the action of the aqueous hormone preparations is evanescent. It is not unusual to

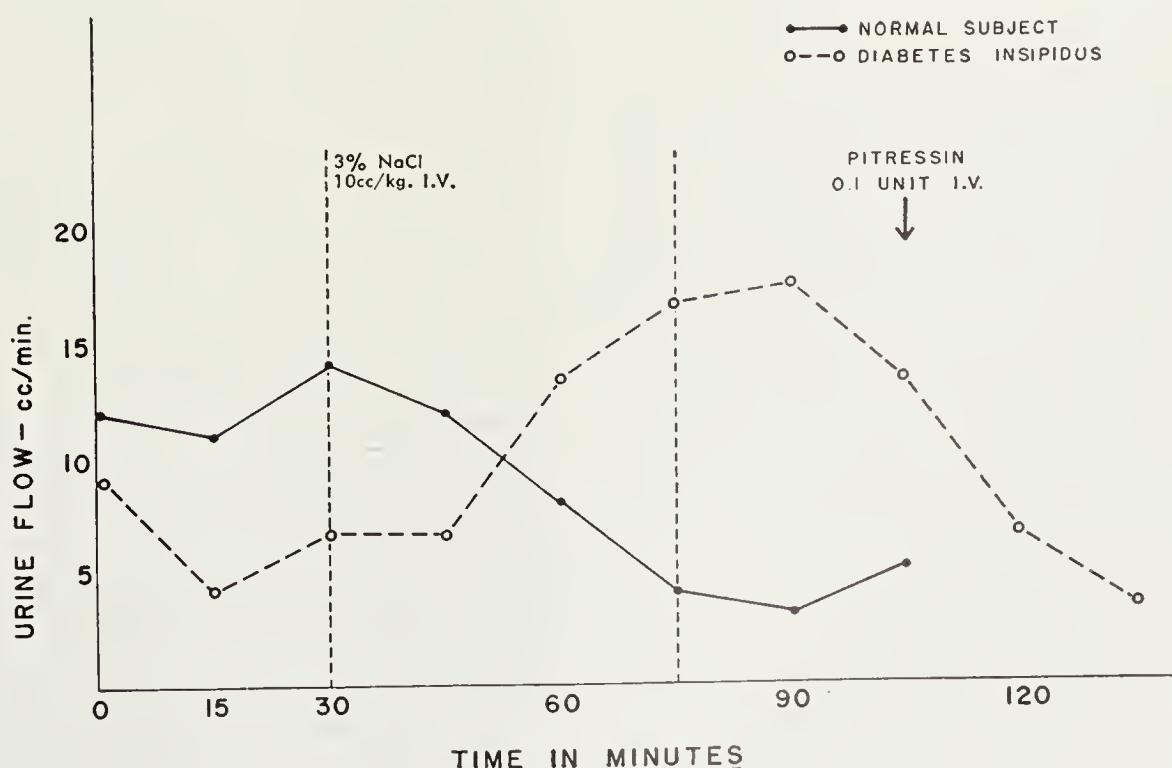


FIG. 102. Hypertonic saline test.

obtain excellent regulation in a serious case with quantities as small as 0.1 to 0.2 ml. of "Pitressin" every four hours. Such frequent injections, however, are impracticable for prolonged treatment. Nasal insufflations of dried posterior pituitary powder (supplied in 5 and 30 Gm. bottles) accomplish the same purpose and are more easily administered, but in some patients result in a chronic rhinopharyngitis and even gastritis from powder which is swallowed.

"Pitressin Tannate in Oil" is supplied in 1 ml. ampuls with a strength of 5 I.U. per ml. This preparation provides relatively long action of the hormone with a single injection administered every 24 to 48 hours. Initially, 0.3 to 0.5 ml. may be given. The minimal dose adequate to control the polyuria and polydipsia is readily established. The hormone is preferably given in the evening to ensure a restful night, since the wearing off of the hormone action is less troublesome during the daytime. *Great care should be employed to caution patients to warm the vial of "Pitressin Tannate" and to shake it repeatedly and thoroughly, since the active material has a tendency to precipitate out in the vial.*

The prognosis of this chronic deficiency syndrome is that of the initiating disease process.

#### EXCESS OF POSTERIOR LOBE HORMONE

Although it is an attractive hypothesis to consider that certain patients presenting edema and oliguria are suffering from a relative or absolute excess of antidiuretic hormone, no well-established clinical entity is accepted. Hyperfunction, if it does occur, is apparently never the result of neoplasm, for the only recorded tumors of the posterior lobe are ganglioneuromas and gliomas, both rare. Evidence of excessive antidiuretic activity consists largely in the demonstration of increased antidiuretic hormone in the urine. It seems reasonable to accept these observations, and recent data tend to confirm the identity of the urinary "antidiuretic" substance with that of the posterior pituitary hormone. It is obvious that an excess of hormone could develop as a consequence of increased secretion or decreased breakdown, the latter being the mechanism postulated in certain patients with liver failure. As in all measurements of urinary hormone excretion, the possibility of a change in renal threshold or excretion of the hormone must be considered.

#### OXYTOCIC ("PITOCIN") FACTOR

Although the oxytocic action of posterior pituitary extract is well established, there are no definitely established clinical diseases or syndromes exhibiting primarily an excess or a deficiency of this factor.

#### MELANOPHORE-DISPERSING HORMONE (INTERMEDIN)

**Introduction.** In 1916 Smith and Allen, working independently, reported that removal of the pituitary anlage in the 4 mm. frog resulted in the production of pale "albino" adult frogs. Later, it was shown by Swingle and by Smith and Smith that this defect could be corrected by the injection of hypophyseal extracts, and that the principle responsible for the darkening effect of the extract was found in greatest concentration in the intermediate portion of the pituitary. It was also shown by the Smiths that the hormone acted by spreading the pigment granules in the pigment-bearing cells or melanophores. The principle was therefore called "melanophore-spreading hormone" or, less correctly, "melanophore-dilating hormone."

Because the hormone is particularly concentrated in the intermediate lobe of the hypophysis, it has also been called by Zondek "intermedin." In those species which do not possess a distinct intermediate lobe, the hormone is found in both anterior and posterior lobes, with the greatest concentration in the posterior lobe. In species where the intermediate lobe does not exist and where the anterior and posterior lobes are anatomically separate (as in the whale, porpoise, armadillo, and chicken), intermedin has been found in greatest concentration in the anterior lobe while, curiously enough, none has been demonstrated in the posterior lobe.

**Chemical Characteristics.** The hormone is soluble in water, and insoluble in acetone and various other organic solvents. It is thermostable but does not resist drying. It is photolabile. In electrophoretic studies it migrates to the cathode. Earlier studies suggested that intermedin possessed an antidiuretic effect, without any toxic or pressor action. At present the antidiuretic action of intermedin is generally thought to be due to contamination with small quantities of vasopressin.

**Clinical Studies: ISOLATION OF HORMONE IN URINE.** The hormone has been recovered from the urine of patients with melanotic sarcoma, hyperthyroidism, cancer, retinitis pigmentosa, and hypophyseal tumors, and from the urine of women in both early and late pregnancy. It appears that the finding of this hormone in the urine is not a sufficiently clearly understood or constant phenomenon to be of diagnostic assistance in these diseases.

**USE OF HORMONE IN THERAPY.** There are a few reports in the literature on the use of intermedin in patients with vitiligo. The hormone has been administered parenterally over a period of months. In general, the results have been inconclusive.

**Summary.** The melanophore-dispersing hormone has a prominent role in the skin physiology of certain amphibia and fishes. In man its role is obscure. Clinical use, either as a diagnostic or as a therapeutic means, has been disappointing.

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# 55

## Diseases of the Thyroid Gland

George W. Thorn and Peter H. Forsham

Introduction  
 Hypothyroidism  
 Hyperthyroidism  
 Exophthalmos  
 Thyrotoxic Myopathy  
 Thyrotoxic Heart Disease  
 Tumors of Thyroid Gland  
 Thyroiditis

### INTRODUCTION

The thyroid gland may be responsible for disorders within the body as a consequence of an increase in gland size and consistency (goiter) or an alteration in hormone secretion. Changes in gland size are due most frequently to toxic and nontoxic goiter, adenomas, thyroiditis, or malignancies. Symptoms arise from local compression in the neck and superior mediastinum. With abnormalities in the secretion of hormone, far-reaching metabolic disturbances occur. The thyroid hormone normally acts as a catalyst or acti-

vator for respiratory cell enzymes involved in oxidative processes generally throughout the body. An excess of hormone induces a significant rise in basal oxygen consumption of the tissues (hypermetabolism). Insufficiency of thyroid hormone is followed by a reduction in oxidative reactions (hypometabolism).

The activity of the thyroid gland appears to be controlled by the anterior pituitary thyrotrophic or thyroid-stimulating hormone (TSH) (see p. 560). As might be anticipated, the level of circulating thyroid hormone affects the secretion of TSH. Reduction in circulating thyroid hormone stimulates the output of TSH, which in turn increases the secretory activity of the thyroid gland. Conversely, increased levels of circulating thyroid hormone tend to depress the secretion of TSH and so in turn retard thyroid activity. It is thought that thyrotrophic hormone

is inactivated by thyroid tissue (and as well by lymphoid and thymic tissue), the most likely mechanism being that TSH contributes some essential part of its molecule to the metabolic processes of the cell as it is being inactivated.

In the biosynthesis of thyroid hormone (fig. 103), iodide or iodine is absorbed into the serum from the gastrointestinal tract only as inorganic iodide and is specifically trapped by the thyroid cells. This trapping mechanism is enhanced by TSH and blocked by thiocyanate. The iodide is then oxidized into iodine, probably within a protein molecule. This step is blocked by thiourea compounds and sulfonamides. The iodine is then combined with tyrosine to form monoiodotyrosine and diiodotyrosine. Two diiodotyrosine molecules are bound in a second oxidative reaction to form thyroxin. Thyroxin and thyroid globulin form the thyroglobulin molecule, presumably through a peptide linkage, and the thyroglobulin so formed is stored in the follicle as colloid. Thyroglobulin itself does not enter the blood stream unless the thyroid gland has been traumatized.

Proteolytic enzymes hydrolyze the thyroglobulin into thyroxin and thyroxin polypeptides. This reaction is enhanced by TSH and inhibited by iodine. The acinar cells appear to secrete thyroid hormone directly into the blood stream as well as to transfer thyroid hormone from the lumen of the follicle through the cells into the

blood stream. The thyroid hormone appears to circulate as a thyroxin-albumin, alpha-globulin, or beta-globulin complex. For practical purposes, the level of organic iodide in the blood (protein-bound iodine, PBI) is a measure of the amount of circulating thyroid hormone. Oral or parenteral thyroxin simulates all of the known actions of endogenous thyroid hormone.

The thyroid gland is capable of increasing or decreasing its functional activity markedly as indicated by changes in total weight, iodine content, blood supply, and microscopic appearance. Most of these changes may be correlated with a response to TSH. In the absence of essential raw material (iodine, for example), or in the presence of a relative iodine deficiency (as may occur during the increased demand period of puberty, pregnancy, and lactation), hormone production is insufficient, and the blood PBI is reduced. In response to a lowered thyroid content of the blood, the output of TSH is increased, and hyperplasia of the thyroid gland follows.

## HYPOTHYROIDISM

**History.** The idea that sporadic cretinism was due to the absence of the thyroid gland was first expressed by Dr. C. H. Fagge at Guy's Hospital in 1871. In 1874, Gull described adult myxedema, stating that it resembled cretinism but came on in adult life. The term "myxedema" or "mucous edema" must be credited to Ord

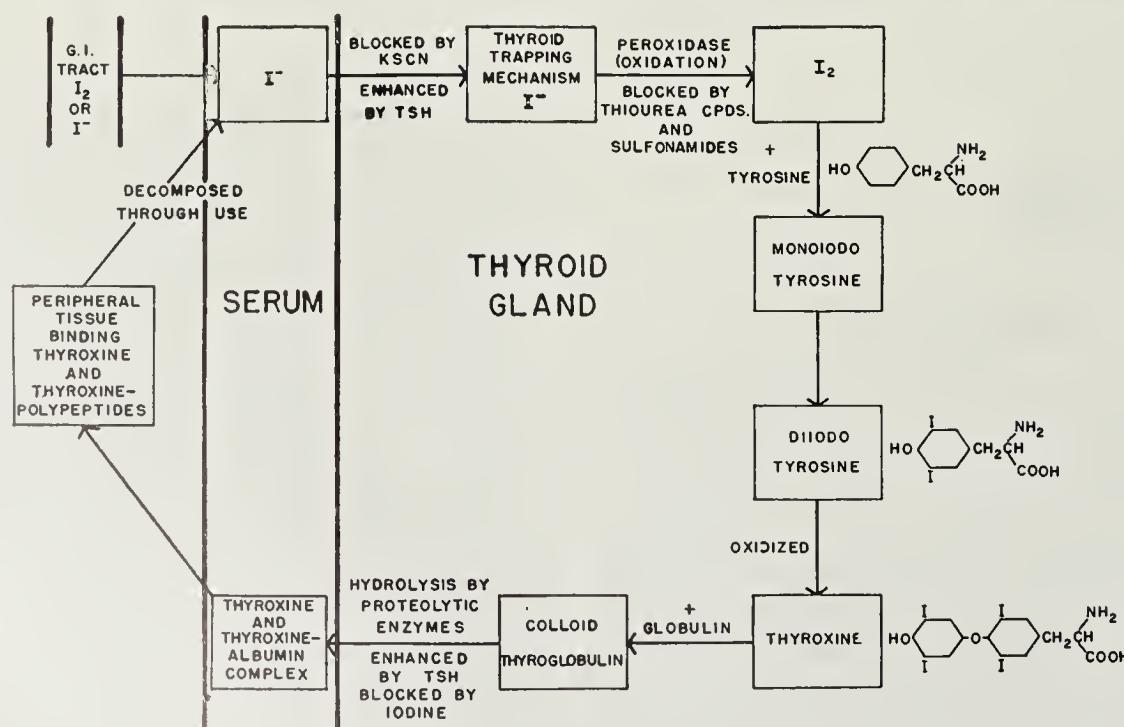


FIG. 103. Metabolic pathway of iodine.

(1878). During the subsequent four to five years the Reverdin brothers of Geneva and Kocher of Berne observed that following thyroidectomy for goiter there appeared what they termed post-operative myxedema or "cachexia strumipriva." In 1891 Murray, an English physician, administered thyroid substance to a myxedematous patient with remarkable improvement. The material employed was a glycerin extract obtained from sheep thyroids. Magnus-Levy, in 1895, observed that thyroid medication was followed by an increase in basal metabolic rate in patients with hypothyroidism. In 1896 E. Baumann obtained an acid hydrolysate of thyroid tissue in powder form which contained 10 per cent of iodine, thus establishing the high iodine content of thyroid. Oswald, three years later, prepared iodothyroglobulin, thus suggesting that the thyroid hormone was a protein substance. A substance termed thyroxin was first isolated by Kendall in 1919 and it was synthesized by Harrington and Barger in 1927.

**Incidence.** Congenital thyroid insufficiency is rare in this country. The incidence of myxedema (juvenile and adult) is estimated to be one in every 1500 hospital admissions. Adult myxedema occurs five times as frequently in females as in males and most frequently between the ages of 30 and 60 years.

**Etiology.** Hypothyroidism may be either primary or secondary. Primary hypothyroidism from birth results in a clinical picture characteristic of cretinism, and is due either to genetic defects—i.e., athyreosis (sporadic)—or to maternal thyroid deficiency (endemic). The occurrence of primary thyroid deficiency later in life gives rise to the syndrome of juvenile or adult myxedema. Under these circumstances, inadequate thyroid hormone is due to destruction of the thyroid gland by disease or surgical removal. Secondary hypothyroidism may occur at any time as a consequence of anterior pituitary failure.

**Physiopathology.** The most frequent cause of hypothyroidism is iodine deficiency or an excess of "goitrogenic" substances in the diet. Endemic cretinism is found among the children of goitrous mothers. Prenatal iodine deficiency rather than a genetic factor appears to be the cause. Under such circumstances, thyroid hormone administered within the first few months of life should correct most of the abnormalities. In sporadic cretinism in which a genetic factor appears to be

responsible rather than iodine deficiency, athyreosis may be accompanied by other defects, particularly in the central nervous system. Under these circumstances early thyroid replacement therapy will not correct all existing defects.

Postthyroidectomy myxedema occurs frequently as compared to the spontaneous variety. Spontaneous myxedema occasionally develops following chronic thyroiditis. Hypothyroidism secondary to anterior pituitary atrophy, necrosis, or tumor may be complicated by adrenal and gonadal deficiencies as well (pituitary myxedema).

**Clinical Picture.** The general appearance is similar in *cretinism* (hypothyroidism from birth) and in *childhood myxedema* (thyroid function present at birth but failing early in life), although, in general, signs of the deficiency are more severe in the former condition than in the latter. This is particularly true of mental retardation. Patients are dwarfed, stocky, and somewhat overweight, with a broad, flat nose; eyes set apart due to failure of naso-orbital development; coarse features; thick lips; protruding tongue; spadelike, stubby hands; and x-ray evidence of retarded bone age, with a decreased serum alkaline phosphatase. In infancy the characteristic facies, the hoarse cry, the large tongue, the pot belly, and the presence of an umbilical hernia should call attention to the diagnosis of hypothyroidism and cretinism. Diagnosis and treatment at the earliest possible date in infancy are important, as the intellectual development which may be anticipated following therapy is directly related to the age at which treatment is instituted. Good results are obtained only when the diagnosis is established early and *adequate* therapy is instituted at once.

The *adult* patient with *myxedema* has a typical facies characterized by a dull, disinterested expression, and puffy eyelids, often with an alopecia of the outer third of the eyebrows. The skin of the face exhibits pallor and a "peach-bloom" coloring over the malar prominences. The skin elsewhere on the body is dry and rough. The subcutaneous tissue is indurated and doughy due to the presence of interstitial fluid of high protein content. The hair is coarse, brittle, and dry. There is swelling of the tongue and larynx, and a halting, slurred, hoarse speech, with slowing of mental and physical activity. There is usually anemia, constipation, and increased sen-

sitivity to cold. There may be vague arthralgic pains and muscular weakness. Female patients with myxedema during the active ovarian cycle usually note prolonged menstrual bleeding.

The heart may be somewhat smaller than normal. When larger than normal there is frequently pericardial effusion. Thyroid tissue is rarely palpable except in the presence of chronic thyroiditis or endemic goiter. Skeletal growth is usually normal in the adult patient with myxedema.

Laboratory examination reveals a low basal metabolic rate (20 to 40 per cent below normal), elevated serum cholesterol (300 to 700 mg. per 100 ml.), low serum protein-bound iodine (less than 2  $\mu\text{g}$ . per 100 ml., normal being 3.5 to 7.5  $\mu\text{g}$ . %), and little if any iodine uptake in the region of the thyroid following the administration of a small tracer dose of radioiodine ( $I_{131}$ ). It is also worth noting that the spinal fluid protein concentration is elevated in patients with well-developed myxedema.

*The diagnosis of myxedema will almost always be suggested by the facial appearance of the patient.*

In hypothyroidism without myxedema the signs and symptoms are less striking. Thyroid tissue may be absent or there may be a goiter present. Patients with mild hypothyroidism may complain of easy fatigability, disturbed emotional control, vague aches and pains, menstrual disturbances, and anemia.

Hypothyroidism secondary to anterior pituitary deficiency may present a picture indistinguishable from that of myxedema. Careful study will usually reveal associated gonadal and adrenal deficiency out of proportion to that seen in primary myxedema. In contrast to patients with myxedema who respond readily and satisfactorily to thyroid extract, administration of this hormone to patients with pituitary myxedema may precipitate adrenal crisis. The administration of pituitary thyrotrophic hormone (TSH) is followed by a rise in serum protein-bound iodine in patients with hypothyroidism secondary to pituitary insufficiency (see Pituitary Myxedema, Chapter 53).

**Differential Diagnosis.** Little difficulty will be experienced in the diagnosis of classic cretinism, juvenile myxedema, or adult myxedema. Occasionally a Mongoloid infant may be confused with a cretin. However, the characteristic Mongoloid eyes and the normal skin and hair texture

distinguish the Mongoloid imbecile from the hypothyroid cretin. Patients with chronic nephritis may simulate juvenile or adult myxedema. This is particularly true of the chronic uremic patient with retarded mental acuity and characteristic facial expression. The difficulty in diagnosis is made more confusing by the fact that hypothyroidism may be present in many of the nephritic patients. Recent studies suggest that hypothyroidism frequently develops in patients with massive proteinuria, supposedly on the basis of loss of TSH or the thyroid-protein molecule in the urine. The urinary findings in nephritis and the evidence of nitrogen retention are however sufficient to establish the primary disorder in such cases.

Not infrequently patients with hypothyroidism exhibit severe anemia, and clinically resemble patients with pernicious anemia. The anemia of hypothyroidism is most often microcytic, occasionally macrocytic and rarely normocytic. It responds only and rather slowly to thyroid medication. Patients with Addison's disease and hypometabolism may be distinguished by the pigmentary changes in the former. The 17-ketosteroid excretion will be low in both conditions. A differential diagnosis may occasionally be established with the use of the 48-hour pituitary adrenocorticotrophin test (p. 595). Not infrequently, severely myxedematous patients fail to respond to 48 hours of ACTH, and do so only after thyroid extract therapy.

The most serious problem in differential diagnosis is that presented by patients with a moderate reduction in basal metabolic rate. *Unfortunately, in the minds of many physicians, hypometabolism and hypothyroidism are synonymous.* The greatest help in differential diagnosis will be obtained from a determination of the protein-bound iodine level of the serum or by studying the uptake of radioactive iodine by the thyroid gland (table 51) or by following the clinical course carefully during the administration of small doses of thyroid hormone (30 to 60 mg. of thyroid [U.S.P.] daily). After two to four weeks the thyroid medication should be stopped, and the cholesterol level followed. In patients with mild hypothyroidism one may not observe a significant elevation in serum cholesterol initially. However, two to four weeks following the termination of one month of thyroid therapy (small dosage), one may expect a rapid rise in serum cholesterol level with an aggrava-

tion of symptoms if the hypometabolic state originally was due to hypothyroidism.

**Treatment.** Desiccated thyroid substance (thyroid [U.S.P.]) is the therapy choice for all types of hypothyroidism except cases due to a specific

Table 51

PERCENTAGE UPTAKE OF RADIOACTIVE IODINE BY THE THYROID AND SERUM PROTEIN-BOUND IODINE IN VARYING STATES OF THYROID FUNCTION

	Hypothyroidism	Euthyroidism	Hyperthyroidism
Radioactive iodine (% uptake)	< 10	10-40	> 35
Serum protein-bound iodine ( $\mu\text{g. \%}$ )	< 3.5	3.5-7.5	> 7.5

iodine lack. In all instances it is desirable to institute therapy with a relatively small dose of thyroid, since a sudden change in metabolic level may induce undesirable psychologic or circulatory disturbances in many patients. It is essential, in the cretin or in juvenile myxedema, to maintain therapy at close to toxic levels in order to ensure optimum growth (table 52). Children

Table 52

AVERAGE DOSE OF DESICCATED THYROID FOR VARIOUS AGE GROUPS

Age	Daily Dose
Infants < 1 year.....	15 mg.
1-3 years.....	30 mg.
3-5 years.....	45- 60 mg.
Adults.....	120-180 mg.

need somewhat more thyroid in proportion to their size than do adults. Dosage usually must be adjusted according to clinical evaluation of the effects obtained, at the same time avoiding symptoms of overdosage such as tachycardia, irritability, continuous weight loss, diarrhea, or sweating. In panhypopituitarism, the initial dose should be small and increased gradually by 15 to 30 mg. increments at three-week intervals. In adults one may begin with a dose of 15 mg. per day, gradually increasing the dose at weekly or biweekly intervals. In patients over 40 to 50 years of age, thyroid therapy should be given cautiously with longer intervals between the increments in dosage. It is wise to begin with 15

mg. daily and to increase the dosage by 15 mg. every two to four weeks. The maximum dose for the most completely myxedematous patients should be 180 mg. per day. In the presence of any evidence of vascular disease, the total dosage should never exceed 30 to 60 mg. daily until the patient has been followed for several months at this dosage level. The maximum effect from a given dosage level will not be obtained for at least 7 to 10 days, and thyroid hormone action will persist for several weeks after the last dose. It is not necessary to give thyroid hormone more than once daily.

## HYPERTHYROIDISM

**History.** It appears that Dr. Caleb H. Parry first described the disease characterized by thyroid enlargement, dilatation of the heart, palpitation, exophthalmos, and nervous and menstrual anomalies. Graves and Basedow, between the years of 1835 and 1843, independently published treatises on the syndrome which now bears their names. That hyperthyroidism was the fundamental disorder in Graves's disease was formulated by Möbius in Germany in 1887. The use of iodine in the treatment of thyrotoxicosis was popularized by Plummer. Recent advances in antithyroid medication concern the use of thiourea derivatives and, within the past few years, the use of radioactive iodine as a therapeutic agent in the treatment of thyrotoxicosis.

**Incidence.** Hyperthyroidism may occur at any age, especially at the time of puberty, pregnancy, and menopause. The disease is much more frequent in females than in males. In nongoitrous areas the ratio of predominance in females may be as high as 4 to 1. In endemic goitrous areas the ratio is smaller. Hyperthyroidism is comparatively rare in children. When it occurs there is usually a diffuse goiter free of nodules.

**Etiology.** At present the cause of thyrotoxicosis is poorly understood. It has been assumed that in patients with exophthalmic goiter (Graves's disease) with diffuse enlargement of the thyroid gland, excessive thyrotrophic hormone might be responsible for the initiation of the syndrome. The not uncommon occurrence of hyperthyroidism associated with acromegaly provides further support for this theory. Convincing proof of this is lacking in most patients; however, in a large number of cases there is a clue in the correlation between episodes of psychic trauma, infections,

injury, or other types of stress at the onset of thyrotoxicosis. In thyrotoxicosis associated with single or multiple adenomas (Plummer's disease), it is evident that the adenoma is occasionally the autonomous source of excess thyroid hormone. In some patients hyperthyroidism occurs without clinical evidence of goiter, and in very rare instances the hyperplastic thyroid tissue may be ectopic.

**Pathology.** In typical Graves's disease the thyroid gland is bilaterally diffusely enlarged, soft, and vascular. The essential lesion is parenchymatous hypertrophy and hyperplasia, characterized by increased height of the epithelium and redundancy of the follicular wall, giving the picture of papillary infoldings and cytologic evidence of increased activity. Such hyperplasia may involve the entire parenchyma of the thyroid or it may be limited to certain areas. The remaining gland may present the picture of the colloid phase of simple goiter or of neoplasia. In some cases the major part of the thyroid tissue is normal or atrophic with one or two hyperplastic adenoma-like nodules which exhibit the characteristic histologic picture. Nodular hyperplasias of this type have been regarded as primary thyroid adenomas and are termed "toxic adenomas" when associated with hyperthyroidism. Approximately three quarters of all cases of thyrotoxicosis show the diffuse type of hyperplasia.

Following iodine medication there is intense colloid storage which often causes enlargement and increased firmness of the gland. Long-continued thyrotoxicosis leads to characteristic lymphocytic infiltration and degeneration of skeletal muscle fibers, enlargement of the heart, decalcification of the skeleton, loss of body tissue including fat depots and tissue protein, but thymic and lymphatic hypertrophy.

**Clinical Picture.** Classic manifestations of thyrotoxicosis include exophthalmos, goiter, fine tremor, increased nervousness, irritability and emotional instability, sweating, and hyperkinesis. Loss of weight and strength usually occur without loss of appetite, although occasionally anorexia, nausea, vomiting, and diarrhea occur. There is intolerance to heat, dyspnea, palpitations, paroxysmal arrhythmias, and not infrequently cardiac failure. Amenorrhea is more common than menorrhagia. Significant physical findings include skin changes, eye signs, cardiac signs, and local changes in the thyroid gland. The skin is warm

and moist with a fine texture, and the hair is soft and silky. Hyperpigmentation is frequently observed. Ocular signs include infrequent winking (Stellwag), lid lag (von Graefe), failure of convergence (Möbius), failure to wrinkle brow on upward gaze (Joffroy), lateral nystagmus (Sainton), tremor of the closed lids (Rosenbach), stare (Dalrymple), vascular congestion of the periorbital region (Topolanski), and difficulty in reverting the upper eyelid (Clifford).

Cardiac findings include wide pulse pressure, tachycardia or auricular fibrillation, frequent systolic murmurs, cardiac enlargement, overt heart failure, and notoriously poor response to digitalization. Local changes in the gland are chiefly diffuse enlargement, audible bruit directly over the gland, and, rarely, signs of tracheal or substernal obstruction.

Childhood hyperthyroidism is relatively uncommon and more closely resembles the physiologic state of increased thyroid activity. It is usually benign, and at least one half of the cases appear to recover spontaneously. Ocular signs are usually absent but in most all instances there is a diffuse goiter with striking tachycardia and other cardiac manifestations. Depending upon the severity of the disease and the caloric intake, growth and development may be either greater or less than normal.

**Diagnosis.** Diagnosis in classic cases of thyrotoxicosis presents little difficulty. In these there are goiter, eye signs, loss of weight, tachycardia, sweating, psychic instability, tremor, increased basal metabolic rate, a high blood protein-bound iodine, and a rapid uptake of radioiodine (table 51). In a few patients the picture may be more of apathy than of hyperactivity, and the basal metabolic elevation may be relatively slight. In such instances the detection of underlying thyrotoxicosis is difficult. All patients with unexplained cardiac failure or irregularities in rhythm should be surveyed carefully for underlying thyrotoxicosis. In patients with cardiac disease, even mild thyrotoxicosis may induce severe disability. The circulation time is characteristically low or normal in the presence of an elevated venous pressure.

Although eye signs are important, it should be recognized that exophthalmic ophthalmoplegia may occur in the absence of thyrotoxicosis and that in certain nationalities such as the Italian, and in certain families, prominent eyes and wide

palpebral fissure occur normally. Exophthalmos is often seen in advanced uremia with normal thyroid function.

Since the basal metabolic rate measures overall oxygen consumption, and not specifically thyroid function, extrathyroid disturbances such as unrecognized infections, leukemia, hypertensive cardiovascular disease, congestive heart failure, perforated eardrums, diabetes, and polycythemia may lead to hypermetabolism without hyperthyroidism. In this circumstance, the serum protein-bound iodine and radioiodine uptake are of value. It is to be noted, however, that the ingestion of thyroid extract will invalidate all of the tests in so far as determining the actual functional capacity of the thyroid gland is concerned. The administration of iodine in any form (cough syrup, radiopaque dyes, salt substitutes, or Lugol's solution) will invalidate the radioiodine uptake, but only organic iodides will invalidate the serum protein-bound iodine. Considerable aid may be obtained, however, from a study of the daily temperature and pulse records. Thyrotoxicosis frequently induces a mild hyperthermia with a very narrow diurnal swing in comparison to the wider changes in temperature from morning to night associated with most infections. The response of the basal metabolic rate, under controlled conditions, to iodine or antithyroid medication is one of the most reliable clinical tests.

**Differential Diagnosis.** Anxiety states may simulate thyrotoxicosis, and in these states tachycardia and weight loss may be pronounced. Frequently, however, there is marked vasomotor instability with cold rather than warm extremities. It is essential to detect underlying thyrotoxicosis in patients with emotional and psychic instability, since the correction of the underlying thyrotoxicosis may be expected to result in great improvement in psychologic and emotional difficulties. In patients of this type basal metabolic determinations are both difficult and unreliable, and one again is forced to employ a more direct determination of thyroid hyperfunction, such as the serum level of protein-bound iodine or the rate of radioiodine uptake following a tracer dose.

**Treatment.** Patients with mild thyrotoxicosis may recover spontaneously, since the disease is characteristically one of cyclical nature. In most instances, however, medical or surgical treatment will be required. Since the etiologic factors responsible for thyrotoxicosis are so poorly under-

stood, all forms of treatment today are directed at reducing the capacity of the thyroid to secrete its hormone.

Effective reduction of thyroid activity may be accomplished by a subtotal thyroidectomy following preparation with iodine or, preferably, propyl thiouracil and iodine. In skilled hands the high rate of cure, the low incidence of complications, and the relatively rapid restoration of an individual to normal are considerations in favor of operation. Preparation of a patient with propyl thiouracil, 100 to 300 mg. in divided doses throughout the 24 hours, administered for two to four weeks, followed by iodine 5 drops of Lugol's solution three times a day for 10 days to two weeks in conjunction with propyl thiouracil, in order to reduce the vascularity of the gland, ensures preoperative control of the thyrotoxicosis in most instances.

The use of iodine in medical treatment is unsatisfactory for even mild cases since the dosage often requires a progressive increase for satisfactory control and patients may be sensitive to iodine. Furthermore propyl thiouracil is ineffective for at least three weeks when given after iodine and one thus faces an escape on iodine unable to combat the thyrotoxic state medically.

Satisfactory regulation of thyrotoxicosis may be obtained with propyl thiouracil and iodine therapy in selected cases. Permanent cure by this method may be anticipated in fifty per cent of the cases when the metabolic level falls well below zero on thiouracil medication and remains there for a prolonged period on moderate doses—100 to 200 mg. daily. In the medical management of thyrotoxicosis, propyl thiouracil may be given for a six to nine month course in a dosage of 50 to 100 mg. every six to eight hours, or a total of 150 to 300 mg. daily. Occasionally it is necessary to increase the dose to 400 mg. daily for satisfactory control. Leukopenia is the principal undesirable side effect to be considered with this group of antithyroid drugs. On rare occasion agranulocytosis occurs suddenly. If the basal metabolic level fails to fall below zero or if it rises rapidly with reduction in drug dosage after six to nine months of therapy, it is probably desirable to resort to surgery. Preparation for this can be accomplished readily by the addition of iodine to the therapeutic program.

If iodine is to be used in combination with thiouracil, care should be taken regarding the

time and frequency of administration. The metabolic circuit of iodine within the thyroid should be blocked by thiouracil at all times, particularly at the time of administering iodine. Since the period of effectiveness of thiouracil may be as short as four hours, escape may occur and active hormone may then be rapidly produced. This will lead to a recurrence or a delay in the subsidence of symptoms.

It is undesirable to give thiouracil to patients with appreciable thyroid tissue in the superior mediastinum, since the enlargement which follows thiouracil therapy may cause distressing symptoms of mechanical obstruction. In most patients, particularly those with cardiac disease, and in patients with other complications which contraindicate surgery, a therapeutic trial with propyl thiouracil is indicated.

More recently it has been suggested that radioiodine may provide an effective medical means of treating thyrotoxicosis. There appears to be no doubt that the avid uptake of radioiodine by the hyperplastic thyroid is a very effective means of administering radiation therapy. With appropriate doses, cure of the thyrotoxicosis is almost certain. The late effects of such radiation therapy remain to be evaluated. At present radioactive iodine therapy should be administered only by those individuals who are equipped and trained in the handling and administration of radioisotopes. It is apparent that x-ray treatment of the thyroid gland, which in the past has been effective in controlling certain patients with thyrotoxicosis, will be displaced almost entirely by the selective action of radioiodine ( $I_{131}$ ).

In all instances, the over-all reaction of the patient, his environment, and his social and economic status form an important basis for evaluating the type of therapy to be employed. A diet of high caloric and vitamin content, rich in carbohydrate, protein, and calcium, and adequate sedation are indicated in both the medical and surgical management of all cases.

**Thyrotoxic Crisis.** The clinical picture of thyrotoxic crisis or storm is that of a fulminating increase in all of the signs and symptoms of thyrotoxicosis. There is usually extreme irritability, delirium or coma, hyperpyrexia up to 106° F. or more, tachycardia up to 200, vomiting, and diarrhea. Rarely, particularly in elderly patients, the clinical picture may be more subtle, with apathy, myopathy, prostration, and coma pre-

dominating, and accompanied by only slight elevation of temperature.

It is extremely unusual to observe thyrotoxic crisis in patients who are properly prepared prior to operation. With the preoperative use of thiouracil and iodine and the capacity to control the metabolic rate, body weight, and nutritional status, postoperative thyrotoxic crisis should rarely if ever occur. If such an event does occur, however, treatment should consist of intravenous administration of large quantities of hypertonic glucose, intravenous administration of iodine, and the continuation of thiouracil administration. The patient should be placed in an oxygen tent, and hyperpyrexia should be treated with ice packs. Sedation with barbiturates may be necessary, and intravenous doses of sodium pentothal may be helpful. Full digitalization should be employed in the presence of cardiac failure.

It is thought that in certain patients thyrotoxic crisis is associated with or precipitated by adrenal cortical insufficiency. The possibility of this coincidence gains support from evidence indicating greatly increased adrenal cortical hormone requirement in experimentally induced thyrotoxicosis and from the poor response of patients with pituitary myxedema treated with thyroid medication alone. Recent studies indicate that, under severe stress such as may occur in thyrotoxic crisis, one should observe a *marked diminution in the number of circulating eosinophils* (less than 25 to 30 per cu. mm.) if adequate adrenal cortical hormone is being liberated (see p. 593). Thus, in a patient with thyrotoxic crisis who has a normal or elevated eosinophil level, one would be justified in administering large doses of aqueous adrenal cortical extract on the basis of probable adrenal cortical deficiency. Fifty ml. should be injected intravenously immediately, and 10 to 20 ml. intramuscularly every hour.

## EXOPHTHALMOS

When exophthalmos becomes the major symptom for concern in Graves's disease, the clinical condition is usually referred to as malignant exophthalmos or hyperophthalmopathic Graves's disease. Clinically there is marked proptosis, lid retraction, and the classic eye signs already described. In addition, there is chemosis of the conjunctiva, edema of the lids, limitation of ocular movements, and diplopia (exophthalmic ophthalmoplegia). The appearance of these latter

signs during the course of Graves's disease is usually a more reliable warning of future serious hyperophthalmopathy than is exophthalmos alone.

It would appear that there are two varieties of exophthalmos in Graves's disease. *Thyrotoxic exophthalmos* occurs with an elevated metabolic rate and is accompanied by an increase in both orbital fat and fat in the extraocular muscles, and is usually accompanied by lid retraction as well. Evidence would suggest that this type is produced by thyroxin, enhanced perhaps by sympathomimetic substances. It is less serious than the second type. *Thyrotrophic exophthalmos* occurs with either a normal or a low metabolic rate, and is accompanied by edema and round-cell deposits within the orbital tissue, occasionally severe enough to obstruct circulation. This probably occurs as a result of the action of an anterior pituitary substance.

In the thyrotoxic variety, the exophthalmos may disappear following treatment of the hyperthyroidism. In the treatment of thyrotrophic or persisting thyrotoxic exophthalmos, thyroid extract or other substances which antagonize or inhibit the production of thyroid-stimulating hormone may be tried. X-ray irradiation to the orbit and pituitary have been tried, with variable success. Finally, orbital decompression by surgery may be necessary. (Naffziger procedure.)

### THYROTOXIC MYOPATHY

Muscular weakness and impairment of muscular function of varying severity often accompany thyrotoxicosis. Certain patients, however, exhibit these symptoms entirely out of proportion to the degree of thyrotoxicosis. The following classification of myopathies associated with thyrotoxicosis has been suggested:

- I. Exophthalmic ophthalmoplegia (described above)
- II. Thyrotoxic myopathy:
  - A. Acute (fulminating progressive myasthenia)
  - B. Chronic thyrotoxic myopathy (myasthenia with muscular atrophy)
  - C. Thyrotoxic periodic paralysis (occasionally occurs in conjunction with familial periodic paralysis)
- III. Myasthenia gravis and thyrotoxicosis

The exact mechanism of thyrotoxic myopathy is not known. It is well known that an increase in creatinuria and a decrease in the creatine and phosphocreatine content of the muscle are common findings in thyrotoxicosis. There appears to be little correlation, however, between the severity of the myopathy and the extent of the creatinuria. There is some evidence that a disturbance of steroid hormone production occurs in patients with thyrotoxic myopathy. Since androgenic hormones are thought to have nitrogen-retaining properties, the hypothesis that the combination of thyrotoxicosis and steroid hormone deficiency can cause myopathy has been suggested.

The treatment is to eliminate hyperthyroidism.

### THYROTOXIC HEART DISEASE

The cardiac manifestations of hyperthyroidism have been described. Many elderly patients present themselves with one or more of these thyrotoxic cardiac symptoms, but without obvious evidence of hyperthyroidism. It is this group of patients that has been called masked or apathetic thyrocardiacs. These patients are occasionally difficult diagnostic problems, but if one keeps thyrotoxicosis in mind the correct diagnosis is almost always made.

In patients with cardiac decompensation and thyrotoxicosis the cardiac output is frequently above normal with a low circulation time in spite of an elevated venous pressure. This has been referred to as "high output failure." Even though elevated above normal, however, the cardiac output, in relation to the metabolic requirements of the body, is abnormally lowered.

There is evidence to suggest that the production of hypothyroidism, and consequently hypometabolism, is beneficial in euthyroid patients with congestive heart failure from any cause, or in those with angina pectoris. This may be accomplished by either surgical thyroideectomy or its medical equivalent, the administration of radioactive iodine.

### TUMORS OF THYROID GLAND

#### SIMPLE GOITER

**History.** Simple goiter has been recognized since antiquity, being described by the Chinese as early as the fifteenth century B.C. and later by the classical Greeks and Romans. Burnt

sponge and seaweed, which are rich in iodine, were used against goiter in the Middle Ages. It was not, however, until the classic experiment of Marine and Kimball was carried out in 1916 on school girls in Akron, Ohio, that iodine was shown clearly to prevent goiter.

**Incidence.** Simple goiter may arise endemically in geographic areas deficient in iodine in soil and water. Endemic areas in the United States are located principally in the Great Lakes basin. Sporadic goiter is most common at puberty, during pregnancy and lactation, or following the menopause. It is 10 times more frequent in females than in males.

**Etiology.** In the presence of an absolute iodine deficiency, as in endemic goiter or with the use of goitrogenic agents, such as cabbage or thiocyanate, the production of thyroid hormone falls off. This is indicated by a lowering of the plasma level of protein-bound iodine (PBI). Such a change may also occur with relative iodine deficiency during periods of increased body demand such as may occur in puberty, pregnancy, or lactation. In response to the lowered PBI the pituitary output of thyroid-stimulating hormone (TSH) is increased, and hyperplasia of the thyroid cells occurs. Noniodized thyroglobulin can be formed, but is inactive, and the colloid is therefore of "poor quality" (basophilic staining and poor in iodine content). Later the colloid disappears, and further cellular hyperplasia occurs. On iodine administration, thyroid hormone is again formed and liberated. The rising blood level of PBI inhibits thyrotoxic hormone production, and there is restoration of active, acidophilic, iodine-rich colloid surrounded by flattened acinar epithelium. From this it may be seen that, early in simple iodine deficiency goiter, the appearance may be that of a colloid goiter; whereas later the histologic appearance might be described as a parenchymatous goiter.

**Pathology.** Pathologically one may observe diffuse enlargement (simple or adolescent goiter) with an increase in the number of cells (parenchymatous goiter) or increase in colloid content (colloid goiter); or the abnormality may be manifest in the development of one or usually many nodules (multinodular goiter) representing an involuntary trend.

**Clinical Picture.** In early simple goiter there is symmetric diffuse enlargement of the thyroid (adolescent goiter), usually associated with no

disturbance of function, although in some instances mild hypothyroidism may occur. In areas of endemic goiter, the diffuse enlargement of the thyroid that occurs in adolescence usually disappears, but if it persists, it almost always becomes nodular if the patient lives long enough. The chief clinical findings include evidence of tracheal or esophageal compression, occasionally with severe obstructive symptoms if the goiter becomes large enough. The recurrent laryngeal nerve compression syndrome is rare, but is noted to produce hoarseness in a few cases. In addition, superior mediastinal compression may occur with large intrathoracic goiters. These multinodular goiters will often lead to hyperthyroidism between the age of fifty and sixty. Malignant tumors occur rarely.

**Treatment.** Iodine in the form of Lugol's solution, fifteen drops three times daily for 2 to 3 months, followed by smaller amounts such as are contained in iodized salt for 6 to 12 months, and desiccated thyroid, 30 to 60 mg. daily, are recommended for the treatment of endemic goiter. The sporadic type does best on thyroid 60 to 120 mg. a day. If this treatment is ineffective, surgical removal should be considered, if obstructive symptoms persist or neoplasia is suspected even though only 1.5 or 3 per cent of unselected cases of nodular goiter proved to be malignant. Thyroid (U.S.P.), 30 to 90 mg. daily, and iodized salt should be given postoperatively for an indefinite period of time, if well tolerated, in an effort to prevent compensatory hypertrophy or nodular development in the remaining thyroid tissue.

## THYROID NEOPLASMS

**Adenomas.** Adenomas of the thyroid may develop at any point from the base of the tongue (thyroglossal duct) to the diaphragm, most commonly within the thyroid itself, however. The growths may vary greatly in size and may be a solitary adenoma or, more commonly, one of several in a multinodular goiter. A good descriptive classification of these adenomas has been suggested by Wegelin:

### I. Fetal adenomas:

- A. Trabecular adenoma
- B. Tubular adenoma
- C. Microfollicular adenoma

### II. Mixed adenoma:

- A. Microfollicular and macrofollicular adenoma

**III. Hyperinvolution (not a true neoplasm):**

- A. Macrofollicular nodule

**IV. Hyperplasia adenoma:**

- A. Papillary adenocystoma

**Malignancy of Thyroid.** Malignancies of the thyroid are pleomorphic and seldom of a pure type. A modification of Warren's classification is given below:

**I. Tumors of low malignancy:**

- A. Adenomas with blood vessel invasion
- B. "Histologic carcinoma" (small tumors found incidentally at operation; without symptoms, recurrence, or metastases)
- C. Papillary adenocarcinoma (occurs in young age group; lymphangio-invasive)

**II. Tumors of moderate malignancy:**

- A. Nonpapillary, solid or alveolar, adenocarcinoma (occurs in older age group; hemangio-invasive; histologically the metastases may appear benign—"benign metastasizing struma")
- B. Hürthle cell adenocarcinoma (occurs in middle age group; usually locally invasive, occasional skeletal or pulmonary metastases)

**III. Tumors of high malignancy (rare):**

- A. Small-cell carcinoma (simplex)
- B. Giant-cell carcinoma
- C. Epidermoid carcinoma
- D. Fibrosarcoma
- E. Lymphoma

**Diagnosis.** The most valuable diagnostic criteria of malignant thyroid growths are rapid increase in size, hard consistency, presence of metastases, fixation to adjacent structures, and hoarseness (laryngeal nerve involvement). A good diagnostic rule to follow is that a hard gland without hypothyroidism is a malignancy rather than chronic thyroiditis. Occasionally metastatic thyroid tumors secrete thyroid hormone.

**Treatment.** It is recommended that nontoxic nodules of the thyroid be removed in persons past the age of 45. Statistics indicate that the incidence of malignancy of the thyroid in the presence of thyrotoxicosis is extremely low—i.e., 1 in 5000 cases.

The treatment of choice in malignant thyroid neoplasms is complete surgical removal of the tumor and regional lymph nodes, followed by x-ray treatment. In some instances the meta-

static lesions may selectively absorb radioiodine. Such selectivity of the metastases may be increased by total thyroidectomy or by treatment with thiouracil. In the presence of this selective absorption, therapeutic radioiodine may be very beneficial.

## THYROIDITIS

Thyroiditis is a comparatively rare disease. It may be acute (suppurative or nonsuppurative), subacute, or chronic.

**Acute Thyroiditis.** This condition may be due to almost any known bacteriologic organism, pyogenic or nonpyogenic. It may follow infection of the mouth, pharynx, upper respiratory tract, or cervical lymph nodes. Very rarely tuberculosis of the thyroid or infection with pyogenic organisms may result in single or multiple abscesses or in suppuration. Classically, there is redness, swelling, and tenderness of the skin over the thyroid, together with fever and other signs of systemic infection. There may be hyperthyroidism and, rarely, thyrotoxic crisis is produced. Therapy consists for the most part in specific chemotherapeutic or antibiotic agents, or x-ray irradiation in nonspecific cases.

**Subacute Thyroiditis.** Subacute or pseudotuberculous thyroiditis is of unknown etiology. It occurs predominantly in middle-aged women and is characterized by rapid, painful swelling of the neck, together with systemic manifestations of inflammation. Therapy consists of x-ray irradiation, thiourea derivatives, and occasionally subtotal thyroidectomy.

**Chronic Thyroiditis.** There are two distinct varieties of chronic thyroiditis: Hashimoto's struma (struma lymphomatosa), and Riedel's struma. Both types are of unknown etiology. Struma lymphomatosa occurs almost entirely in middle-aged to elderly women, and is characterized by a moderately rapid, firm, usually bilateral swelling of the gland. Therapy consists of subtotal thyroidectomy. In Riedel's struma there is a moderately rapid, firm swelling of the gland, producing a hard, indurated enlargement. The gland is irregular, hard, and bound down to surrounding structure, suggesting thyroid cancer. However, there is no involvement of the skin or the regional lymph nodes. Riedel's struma is occasionally associated with hypothyroidism, whereas thyroid cancer rarely is. Therapy for this type of thyroiditis is usually conservative, partial thy-

Table 53

## DIFFERENTIAL DIAGNOSTIC FEATURES OF SUBACUTE THYROIDITIS, RIEDEL'S STRUMA, AND HASHIMOTO'S STRUMA

	<i>Riedel's Struma</i>	<i>Hashimoto's Struma (Struma Lymphomatosa)</i>	<i>Subacute Thyroiditis (Pseudotuberculous)</i>
Age.....	About 50	Late forties, early fifties	Mid-forties
Sex.....	Predominantly female (not uncommon in males)	Predominantly females (rare in males)	Females 6:1
Duration.....	Usually 1 year	Usually 1 year	Usually 8 weeks
Thyroid gland.....	Bilateral, hard, nodular, non-tender, moderately enlarged	Bilateral, firm, occasionally nodular, nontender, moderately enlarged	Bilateral, hard or firm, symmetric, tender, moderately enlarged
Pain.....	Rare	Rare	Common
Pressure symptoms.....	Moderately common	Rare	Common
Fever.....	Absent	Absent	Present
BMR.....	Usually normal, occasionally hypothyroid	Usually normal	Usually normal, occasional hyperthyroidism, early
Sed. rate.....	Usually normal	Usually normal	Usually elevated
Pathology.....	Dense fibrous tissue with chronic inflammatory cells (especially plasma cells and lymphocytes). Few remaining thyroid acini	Dense infiltration by lymphocytes with numerous follicles. Acidophilic degeneration of acinar cells	Dense, cellular, connective tissue proliferation with formation of tubercles containing giant cells. Clusters of polymorphonuclears
Treatment.....	Partial thyroidectomy	Subtotal thyroidectomy	X-ray therapy, thiourea derivatives, thyroidectomy

roidectomy in order to eliminate or relieve fibrous compression or constriction of the surrounding neck structures (table 53).

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## 56

## Diseases of the Parathyroid Glands

George W. Thorn and Peter H. Forsham

Introduction  
Anatomy  
Parathyroid Hormone  
Hypoparathyroidism  
Pseudohypoparathyroidism

Hyperparathyroidism  
Secondary Hyperparathyroidism  
Acute Parathyroid Intoxication  
Tumors of Parathyroid Glands

**Introduction.** The parathyroid glands were first recognized as separate structures and described by Sandström in 1880. In earlier experi-

mental studies concerning the effect of thyroidectomy, changes now known to be due to parathyroid removal were attributed to loss of the

thyroid. The classic experiments of MacCallum and Voegtlin in 1908 clarified this situation. Regulation of calcium and phosphorus metabolism appears to be the chief function of the parathyroid glands, and the activity of the glands seems to be controlled primarily by the serum concentration of these electrolytes. Convincing evidence of a pituitary-parathyroid trophic hormone has not as yet been presented. Further proof of the endocrine nature of these glands followed the preparation of active parathyroid extracts by Collip in Canada and by Hanson and Berman in the United States. Although the mechanism of action remains as yet unknown, parathyroid hormone has been shown to increase urinary phosphate excretion and to lower serum phosphorus levels while at the same time increasing serum calcium levels and urinary calcium excretion. Evidence suggests that the hormone exerts a direct action on the mobilization of calcium from bone as well as the regulation of the renal excretion of phosphorus.

**Anatomy.** The parathyroid glands originate from the posterior halves of the third and fourth pairs of pharyngeal pouches. Therefore, like the thyroid, the parathyroids are entodermal in origin. In man the parathyroids are reddish or yellowish brown and are flattened, ovate, or pyriform bodies located on the posterior surfaces of the lateral lobes of the thyroid, near their medial edges. There are normally four glands. The number may vary from 2 to 10 and their location is extremely variable, having been described in scattered regions of the neck, within the thyroid gland, and in the mediastinum.

In the glands from adult humans, chief cells and oxyphil cells are distinguishable. The chief cells are the more numerous and probably are the source of the parathyroid hormone. Another cell, the large water-clear cell (*wasserhelle* cell) derived from the chief cells, is the commonest cell type observed in hypertrophy and hyperplasia of the parathyroids.

**Parathyroid Hormone.** There is little evidence that the anterior pituitary produces a "trophic" hormone which stimulates the parathyroid glands. The parathyroid hormone regulates calcium and phosphorus metabolism. The most generally accepted mechanism of action of parathyroid hormone is a primary effect on phosphorus metabolism. The hormone increases the excretion of phosphorus in the urine; this in turn

decreases the serum phosphorus level. To maintain the saturation of these salts in the blood, more phosphorus, and with it more calcium, are drawn from bone; as a result, the serum calcium is elevated. When this serum level becomes sufficiently elevated, hypercalcemia occurs. Secondary to these mineral changes an alteration in bone structure and a decrease in bone tissue is produced. A low serum calcium level stimulates the parathyroid glands to increase their hormone production. A primary effect on bone tissue and thereby on calcium metabolism has also been ascribed to parathyroid hormone. Although the evidence for this is not so strong as for the phosphorus-regulating mechanism, it seems quite likely that this mechanism also may be involved to some extent (see Chapter 65).

## HYPOPARTHYROIDISM

**History.** Tetany, a condition resulting from total or extensive parathyroideectomy, received its name from Corvisart in 1852. MacCallum and Voegtlin in 1908 showed that the mechanism of this type of tetany was dependent upon hypocalcemia. The Swiss surgeons, Reverdin and Kocher, in 1882, described postoperative tetany after a complete thyroidectomy for goiter without realizing that the condition was due to parathyroid deficiency.

**Incidence.** Cases of primary parathyroid deficiency are extremely rare. In most instances clinical evidence of parathyroid deficiency is secondary to thyroidectomy. During the past decade increased knowledge and experience in surgical technics have decreased the incidence of permanent parathyroid deficiency secondary to thyroidectomy. Transient deficiency is not unusual and is attributed to temporary interference with the blood supply to the remaining parathyroid glands.

**Etiology.** The most common cause of parathyroid deficiency is operative damage or removal in conjunction with thyroidectomy. Congenital absence of the gland or damage secondary to hemorrhage or infection is rare.

**Pathology.** Aside from more or less complete removal or destruction of the gland surgically, the most common pathologic finding is hemorrhage into the glands of the newborn. Inflammatory reactions or tumors are rare. Persistent severe hypoparathyroidism is frequently associated with lenticular cataracts.

**Pathologic Physiology.** There is a pronounced disturbance of calcium and phosphorus metabolism as reflected by serum calcium levels as low as 2.5 mEq. per liter and serum inorganic phosphorus levels as high as 3-4 mM. per liter.

**Clinical Picture.** The most striking symptom is an increase in neuromuscular excitability dependent upon a decrease in the ionized fraction of calcium in the serum. This leads to muscular cramps, spasm, or more generalized tetany. Painful tonic and clonic convulsions may occur intermittently, accompanied by paresthesia. Tetany is manifested in a stiff, hollowed hand with rigid fingers, flexed at the metacarpophalangeal joints; flexed wrists and elbows; and extended legs and feet. The glottis and larynx are also affected, sometimes causing whistling inspiration (laryngismus stridulus). On occasion this may be fatal in children. Increased neuromuscular irritability may be demonstrated by a light tap over the plexus of the facial nerve (Chvostek's sign). The electrocardiogram may show prolongation of the Q-T interval. Cataracts are present in most cases of long-standing duration, and localized areas of calcification in brain tissue are not unusual. In spontaneous primary hypoparathyroidism, extensive ectodermal changes involving particularly the nails and hair may be seen. The nails may show atrophy or transverse ridging, or present features suggestive of a fungous infection. The hair is likely to be thin, prematurely gray, and even absent in the axillary and pelvic areas. The bones in hypoparathyroidism are definitely more dense than normal. (See Chapter 71.)

Chronic hypoparathyroidism, like acute hypoparathyroidism, usually follows thyroidectomy; but, unlike the acute type, it may vary in severity, may appear spontaneously, and often has no tetany associated with it. The symptoms are not only mild but varied and vague. There may be only latent tetany, fatigue and muscular weakness, gastric intestinal irritability, attacks of unconsciousness, mental retardation, palpitation, numbness of the extremities, or disturbances in growth of the nails. The diagnosis of chronic hypoparathyroidism is usually suspected where certain unexplainable syndromes occur, particularly in thyroidectomized individuals.

**Differential Diagnosis.** The principal causes of tetany are hypocalcemia and alkalosis. Of the nonparathyroid causes of hypocalcemia, rickets,

osteomalacia, steatorrhea, and renal insufficiency with phosphate retention are the most important. In rickets, osteomalacia, and steatorrhea, a low value for serum calcium is almost invariably associated with a normal or low value for serum phosphorus. In late-stage renal insufficiency with hypocalcemic tetany, the elevation in serum phosphorus level is disproportionately higher than that which occurs with a given level of hypocalcemia in parathyroid tetany.

Alkalosis causes tetany with no demonstrable change in the concentration of calcium in the serum. Alkalosis may be due to hyperventilation, to prolonged vomiting of acid gastric contents, or to excessive alkali ingestion. With hyperventilation, the carbon dioxide content of the serum is reduced; whereas, with vomiting and alkali ingestion, the carbon dioxide-combining power of the serum may be increased greatly (see Chapter 29). Alkalotic tetany occurs most frequently in association with acute infections, particularly in children.

Under certain circumstances, patients with marked emotional disturbances may develop transient episodes of tetany with little or no effective hyperventilation and without significant change in the concentration of either serum carbon dioxide or ionized calcium. With this type of tetanic manifestation, in the absence of alkalosis or hypocalcemia, the mechanism is assumed to be mediated directly by the central nervous system through a release of cerebral cortical inhibition as a manifestation of a marked emotional response.

**Treatment.** The object of treatment is to increase and maintain the serum calcium at an approximately normal level. Immediate correction of hypocalcemia may be accomplished by intravenous injection of calcium chloride (10 ml. of a 5 per cent solution) or calcium gluconate (10 ml. of a 10 per cent solution) (see table 54). The effect may be transitory, lasting only a few hours. Injections of parathyroid hormone give more prolonged action (12 to 24 hours). Parathyroid extract is available in injectable form, containing 80 to 120 U.S.P. units per ml. Ten to 50 units per day are usually required. However, this type of treatment eventually loses its effectiveness because of the development of refractoriness. The most satisfactory method of restoring a normal calcium level over a prolonged period is the oral administration of dihydrotachysterol, a de-

*Table 54*  
CALCIUM-REGULATING COMPOUNDS

Type	Route of Administration	Dosage	Effect on Serum Calcium
Calcium chloride (U.S.P.) (36% calcium)	Intravenous	10 ml. of 5% aqueous solution (very slowly)	Immediate but only of short duration
	Oral	10 ml. of 30% aqueous solution, well diluted (2-3 times daily)	
Calcium gluconate (U.S.P.) (9% calcium)	Intravenous	5-20 ml. of 10% aqueous solution (slowly)	Immediate but only of short duration
	Intramuscular	10 ml. of 5% aqueous solution (1-2 times daily)	
	Oral	10-25 Gm. daily	
Calcium lactate (U.S.P.) (18% calcium)	Oral	10-15 Gm. daily (as a clear solution)	Immediate but only of short duration
Dihydrotachysterol (A.T. 10)	Oral	3-4 ml. (1.25 mg. per ml.) daily initially; 1 ml. (3-5 times weekly) as maintenance	Delayed, with a maximum in 48 hours. Prolonged effect
Calciferol (vitamin D <sub>2</sub> ) . . . . .	Oral	100,000-400,000 units daily	Delayed. Prolonged effect
Parathyroid extract . . . . .	Subcutaneous or intramuscular	100-300 units in severe tetany and then 20-40 units every 12 hours. Not recommended for maintenance	Moderately rapid, with maximum in 8-18 hours

ivative of ergosterol known as A.T. 10. The action of A.T. 10, like that of vitamin D, is to increase calcium absorption from the gastrointestinal tract and increase phosphate excretion in the urine. However, the effect of A.T. 10 on the latter is greater than that of vitamin D therapy, more closely simulating the action of parathyroid hormone. One ml. (1.25 mg.) three times daily may be given until a normal serum calcium level has been attained. After that the dose should be reduced to 1 ml. daily. Because of its prolonged action, the serum calcium level must be followed carefully until the exact maintenance dose has been well established, as toxic manifestations follow hypercalcemia induced by excessive A.T. 10 administration. A simple, practical method of regulating the dosage is the use of the urine Sulkowitch test. To perform the test, about 5 ml. of urine is placed in a test tube and about 2 ml. of Sulkowitch solution<sup>1</sup> is added, and the speed (3 to 30 seconds) of

appearance and the degree of density of the dispersed white precipitate are noted. The results are recorded as zero or 1, 2, 3, or 4 plus. A negative test indicates hypocalcemia (less than 3.5 mEq. per liter); a 3 to 4 plus test suggests hypercalcemia (more than 5.2 mEq. per liter). This estimation of calcium can be performed easily by the patient, and the dosage of the medication adjusted depending on whether the test indicates little calcium in the urine or hypercalcemia. Supplementary calcium preparations may be given by mouth. Of these, calcium chloride is the most effective. It may be administered in a dose of 10 ml. of 30 per cent solution, well diluted, three times daily after meals (see table 54).

In acute or severe tetany it is desirable to begin treatment with all four types of medication at once—i.e., calcium intravenously and by mouth, parathyroid extract every 6 to 12 hours, and A.T. 10. Thus the immediate correction of hypocalcemia is accomplished by the use of intravenous calcium, after which parathormone is adequate until the slower and more prolonged

<sup>1</sup> Sulkowitch solution: Oxalic acid, 2.5 Gm.; ammonium oxalate, 2.5 Gm.; glacial acetic acid, 5.0 ml.; and distilled water, q.s. ad 150 ml.

action of A.T. 10 and calcium by mouth becomes effective.

**OTHER MEASURES.** While the various chemical agents have been particularly effective in the therapy of hypoparathyroidism, the institution of certain adjunctive measures will reduce the requirement for medications and, in certain instances, may in themselves control the disorder. The diet should include a high intake of calcium and a low intake of phosphorus. By the use of aluminum hydroxide (8 ml. three times daily) an insoluble aluminum phosphate salt is formed which decreases the phosphate absorption. Foods with a high phosphorus content are to be avoided. These include milk, cheese, egg yolk, cauliflower, and molasses.

During pregnancy it is not uncommon for parathyroid insufficiency to become worse as a result of the fetal demand for calcium. Therefore, all maintenance therapy including calcium will have to be increased during this period.

#### PSEUDOHYPOPARTHYROIDISM

The first description of this rare condition was given by Albright and his co-workers in 1942. Only 10 cases have been reported. While the chemical studies are identical with those described in hypoparathyroidism—namely, hypocalcemia and hyperphosphatemia—in pseudo-hypoparathyroidism there is no chemical response to administered parathyroid hormone. Deficiency of parathyroid hormone is apparently not the cause, but rather a lack of responsiveness by the tissue end organs. Exploration for parathyroid tissue performed in a few cases of pseudo-hypoparathyroidism has revealed either normal or hyperplastic parathyroid tissue. Observed in association with the parathyroid hormone refractoriness are certain physical features—i.e., round face, short stature, and shortening of the metatarsal and metacarpal bones (index finger may be longer than middle finger).

**Diagnosis.** Because of frequent history of convulsions the condition may be incorrectly labeled epilepsy. The symptomatology, chemical findings, and physical signs are those of hypoparathyroidism. The resistance to parathyroid extract as measured by failure to produce a phosphate diuresis (Ellsworth-Howard test) serves to distinguish it from hypoparathyroidism.

**Treatment.** The same treatment as outlined under hypoparathyroidism, with the exceptions

that one must keep in mind the existence of unresponsiveness to parathyroid extract and that occasionally a diminished responsiveness to A.T. 10 is found. Vitamin D and supplementary oral calcium are effective and inexpensive (table 54).

#### HYPERPARATHYROIDISM

**History.** Generalized osteitis fibrosa cystica, a disease of the bones, was described in 1891 by von Recklinghausen. In 1925 Mandl removed a parathyroid adenoma from a patient suffering from this disease and noted a remarkable improvement. The clinical and metabolic studies subsequently carried out by Albright, Bauer, Aub, and Cope are classic.

**Incidence.** Some authors believe that 5 to 10 per cent of all kidney stones may be associated with hyperfunction of these glands. The disease occurs most frequently in middle life, and about 70 per cent of the reported cases are females. The exact incidence of the disease is unknown but, due to the work of Albright and his colleagues, there has been a more deliberate search for the disease with a consequent increase in the frequency of diagnosis. These investigators were able to show (1) that hyperparathyroidism can occur without evident disease of bone, (2) that hyperparathyroidism is relatively common, and (3) that involvement of the urinary tract is more common than involvement of the skeleton. It is now clear that disease of bone represents a relatively late development in hyperparathyroidism and that the disease may manifest itself in other ways.

**Etiology.** The most common cause of hypersecretion of the parathyroid glands is an adenoma (in approximately 88 per cent of cases), while diffuse parathyroid hyperplasia or hypertrophy occurs rather infrequently in cases of primary hyperparathyroidism.

**Pathology.** An adenoma may involve all or part of the gland, and either type of cell or an intermediate type. Adenomas are especially prone to occur in ectopic glands. In 90 per cent of the cases single glands are involved. Skeletal lesions observed in conjunction with long-standing hyperparathyroidism include generalized decalcification of the bones with an increase in osteoclasts, osteoblasts, and fibrous tissue which may lead to the formation of osteoclastomas and multiple cysts with fibrous walls. Fractures occur frequently, and the long tubular bones are

the earliest and most extensively involved. Degenerative changes occur in other tissues (i.e., renal tubular epithelium, heart muscle, and gastric mucosa), and often are followed by calcification. Fifty per cent of the cases show some evidence of renal damage such as nephrolithiasis, pyelonephritis, and calcium deposits in and around the tubules.

**Pathologic Physiology.** Characteristically, the serum calcium is elevated and may attain values as high as 9 mEq. per liter (18 mg. %). The serum inorganic phosphorus level is reduced below 2 mEq. per liter (3.1 mg. %) unless renal damage has resulted in secondary phosphorus retention. The excretion of calcium and phosphorus in the urine is increased. With extensive bone involvement, the alkaline phosphatase may reach levels as high as 20 to 30 Bodansky units.

**Clinical Picture.** The earliest symptoms rarely lead to a diagnosis. They may be recognized in retrospect as an accompaniment of hypercalcemia, and include muscular weakness, hypotonia, anorexia, nausea, constipation, and bone pain. Polyuria and polydipsia indicate renal complications. Often the first indication of hyperparathyroidism is an attack of renal colic or a spontaneous fracture. Long-continued action of excessive parathyroid hormone leads to skeletal thinning of all bony structures except the teeth. A more complete discussion of the relationship between the parathyroid glands and bone disease is given in Chapter 69.

**Diagnosis.** Classic cases of hyperparathyroidism (*osteitis fibrosa cystica* or *von Recklinghausen's disease*) are usually diagnosed easily from the clinical picture just described and the chemical findings of hypercalcemia, hypophosphatemia, excessive calcinuria on a low calcium intake, and an increased serum alkaline phosphatase activity. It is important to carry out simultaneous calcium and total protein determinations, as marked hypoproteinemia (with accompanying decrease in calcium proteinate) may mask an increase in diffusible ionized calcium, the fraction of importance in this disease. While neither the protein nor the ionic fraction can be measured directly, both can be estimated from the concentration of total calcium and total protein by use of the readily available nomogram of McLean and Hastings. Also, in hypercalcemic states other than hyperparathyroidism the cerebrospinal fluid calcium is equal

to the diffusible fraction of normal serum; it is affected little by uremia, parathyroidectomy, or parathyroid extract. In a few cases, bone lesions may be absent or minimal where calcium and protein intake have been high and the disease relatively mild or of short duration.

**Differential Diagnosis.** Careful observation may be required to differentiate less typical cases from the following skeletal disorders:

1. **OSTEOPOROSIS.** Here the formation of bone is decreased due to failure of osteoblasts to form a matrix. Calcium, phosphorus, and alkaline phosphatase are normal, though urine calcium may be increased early. This is frequently seen in women after menopause and involves spine and pelvis, very rarely the skull. The lamina dura about the teeth persists.

2. **OSTEOMALACIA.** This implies failure to mineralize the matrix, seen especially in steatorrhea and vitamin D deficiency. Both serum calcium and phosphorus and urine calcium are decreased, while serum alkaline phosphatase is increased. Other signs of avitaminosis may be seen.

3. **PAGET'S DISEASE.** This presents circumscribed lesions by x-ray with coarse trabeculae, bony expansion, and sharp demarcation. Calcium and phosphorus are normal, while the phosphatase may attain its highest values. A bone biopsy may be necessary to establish the diagnosis.

4. **POLYOSTOTIC FIBROUS DYSPLASIA.** This has a regional distribution of *osteitis fibrosa* accompanied by precocious puberty in females, a brownish skin pigmentation, occasional hyperthyroidism, and normal chemistry. X-ray may show density as well as fibrosis.

5. **MULTIPLE MYELOMA.** This condition may show sharp demarcation of bone lesions by x-ray, with increased serum and urine calcium, possibly stones, a variable phosphorus level, increased globulin, Bence-Jones protein (50 per cent), and plasma cells. A sternal bone marrow biopsy may provide the diagnosis.

6. **METASTATIC MALIGNANCIES.** These may present a variable x-ray picture, depending on whether the origin of the primary tumor is breast, prostate, hypernephroma, bronchus, or thyroid. Serum calcium and alkaline phosphatase may be increased. An increase in serum acid phosphatase is presumptive evidence of metastatic bone disease from prostatic cancer.

7. RENAL RICKETS. In this condition there exists a history of onset of renal difficulties prior to skeletal changes. Acidosis and increased serum chloride level are present if vomiting has not occurred.

8. OTHER DISEASES. Gaucher's disease, Niemann-Pick disease, Hand-Schüller-Christian syndrome, Hodgkin's disease, osteogenesis imperfecta, osteomyelitis, sarcoid, xanthomatosis, chronic radium poisoning, polycythemia vera, erythroblastosis, etc., may have to be considered in the differential diagnosis.

A more complete discussion of these individual skeletal disorders is given in Section 3.

*Hypercalcemia Associated with Renal Insufficiency and Prolonged Milk or Alkali Ingestion.* Burnett and his co-workers (1949) described a syndrome with many features common to primary hyperparathyroidism and secondary renal damage. The characteristic features in patients with this syndrome were a history of prolonged and excessive intake of milk and absorbable alkali; hypercalcemia without hypercalciuria or hypophosphatemia; marked renal insufficiency; calcinosis; and mild alkalosis. Treatment consists of a low-milk, low-alkali diet and a high fluid intake. While the azotemia and hypercalcemia may diminish and the chemical imbalance may become restored to normal, the prognosis is unfavorable.

*Vitamin D Intoxication.* Excessive vitamin D administration induces a clinical and pathologic picture similar to hyperparathyroidism. The hypercalcemia produced appears to represent calcium mobilized from bone. The symptoms of intoxication are fatigue, weight loss, and vomiting. Impaired renal function, and metastatic calcifications, particularly of conjunctiva and cornea, are observed. Recovery depends upon the severity of the toxicity and promptness of withdrawal of the vitamin D.

*Testosterone- and Estrogen-Induced Hypercalcemia.* The administration of large doses of sex hormones for treatment of osteolytic lesions associated with malignancy may produce hypercalcemia and secondary nephrocalcinosis. Gastrointestinal symptoms and symptoms of renal insufficiency predominate.

**Treatment.** Once the diagnosis of primary hyperparathyroidism is established, fluids should be forced, intake of milk restricted, and surgical consultation obtained with a view toward explor-

ation. Difficulty in locating the offending gland because of inconstant anatomic positions may necessitate not only extensive but also repeated surgery. Removal of an adenoma or removal of all except a portion of one gland in case of hypertrophy and hyperplasia may be expected to cure the condition. When serum alkaline phosphatase is markedly elevated, a two-stage operation may be performed or large quantities of calcium given intravenously to prevent tetany. In the presence of severe renal damage, less parathyroid tissue is removed. A diet high in calcium, phosphorus, and vitamin D is given postoperatively. Under normal circumstances great improvement in the skeletal changes may be anticipated. Improvement in renal function may also occur.

## SECONDARY HYPERPARATHYROIDISM

**History.** The existence of enlargement of the parathyroid glands secondary to another disease process in the body was first noted in 1905 by MacCallum in a case of nephritis. One year later, Erdheim noted similar findings in rickets, and since that time the syndrome of secondary hyperfunction of the parathyroids has been recognized.

**Incidence.** As a complication of advanced renal disease, hyperfunction of the parathyroids is relatively common. In 1935 Pappenheimer and Wilens reported that in a series of 21 cases of nephritis the mean parathyroid weight was 50 per cent greater than that in a control group.

**Etiology.** The most common cause of this condition is chronic longstanding renal disease as in glomerulonephritis, pyelonephritis, and, in children, congenital anomalies of the genitourinary tract with the resultant so-called renal rickets. Reports of secondary hyperparathyroidism have been noted in a variety of diseases such as osteogenesis imperfecta, Paget's disease, multiple myeloma, carcinoma with bone metastases, and pituitary basophilism.

**Pathology.** The parathyroid glands are enlarged diffusely and are hyperplastic. No single adenomas are visible. The cells are normal in size and easily differentiated from those seen in primary hyperparathyroidism. The former are principally chief cells with some increase in oxyphil cells, as opposed to the huge, water-clear cells of primary hyperparathyroidism. The bone lesions are entirely similar to those seen in primary hyperparathyroidism—namely, general-

Table 55

## SUMMARY OF CHEMICAL FEATURES OF DISEASES WITH DISTURBED CALCIUM AND PHOSPHORUS METABOLISM

	Serum			Urine*		Feces*	
	Ca	P	Alkaline Phosphatase	Ca	P	Ca	P
Hyperparathyroidism.....	Increased	Decreased	Increased	Increased	Increased	Normal	Normal
Paget's disease.....	Normal	Normal	Increased	Normal	Normal	Normal	Normal
Hypoparathyroidism.....	Decreased	Increased	Normal	Decreased	Decreased	Normal	Normal
Renal insufficiency.....	Decreased	Increased	Normal	Decreased	Decreased	Increased	..
Osteomalacia.....	Decreased or normal	Decreased	Increased	Decreased	Decreased	Decreased	Decreased
Senile osteoporosis.....	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Multiple myeloma.....	Normal to increased	Normal	Normal	Normal to increased	Normal to increased	..	..
Hypocalcemia and excess alkali intake (Burnett's syndrome)	Increased	Normal to increased	Normal	Normal	..	..	..
Vitamin D intoxication...	Increased	Increased	Normal	Increased	Increased	Decreased	Decreased
Metastatic carcinoma.....	Normal to increased	Normal	Normal to increased	Increased	Increased	..	..
Hyperventilation (alkalosis).....	Normal	Normal	Normal	Normal	Normal	..	..

\* On low-calcium diet.

ized decalcification and bone cysts, with or without outright fracture.

**Pathologic Physiology.** The presence of long-standing phosphate retention in renal disease is the *sine qua non* for the development of the syndrome. Drake, Albright, and Castleman produced the disease in rabbits by the administration of parenteral phosphates. It is suggested, therefore, that the effect of high serum inorganic phosphorus acts by depressing the level of circulating ionized calcium, resulting in a stimulation of the parathyroid secretion. Indeed, in these cases the serum calcium may be low early in the disease and ultimately reach the heights seen in primary hyperparathyroidism.

**Clinical Picture.** The symptoms are usually those of the primary disease process before any evidence of hyperparathyroidism is noted. Classic glomerulonephritis or pyelonephritis, uremia, and evidence of renal insufficiency dominate the clinical picture. In children dwarfism and pathologic fractures may be the presenting complaints.

**Diagnosis.** The chemical findings of hypercalcemia or normal calcium with hyperphosphatemia, and high serum alkaline phosphatase, with the classic skeletal x-rays of bone cysts and generalized demineralization lead to the diagnosis of parathyroid hyperfunction with renal

disease. The history of early renal disease is often the only differential diagnostic point, since the primary cases are often complicated late in the disease by renal failure secondary to longstanding hyperparathyroidism. In cases of multiple myeloma the entire picture may be indistinguishable from primary and secondary hyperparathyroidism. It is only the finding of Bence-Jones protein and myeloma cells in the marrow that makes the differential diagnosis clear. The other entities mentioned are rare and have characteristic bone lesions—i.e., osteogenesis imperfecta and Paget's disease.

**Treatment.** Of greatest importance is the establishment of the diagnosis. Once this is accomplished, all therapy is directed at the primary disease and an attempt is made to diminish the intake of phosphate by oral administration of aluminum hydroxide and by reduction of milk consumption. In addition, fluid is forced. In rare cases the parathyroids have been surgically removed with little benefit, the patient ultimately dying of the primary renal disease.

#### ACUTE PARATHYROID INTOXICATION

This rare clinical condition occurs as an acute complication of hyperparathyroidism and is

characterized by weakness, lethargy, and intractable nausea and vomiting, an extreme elevation of the serum calcium level, gradual elevation of serum phosphorus, and finally coma and sudden death. The discovery and removal of a hyperfunctioning parathyroid tumor offers the only chance of survival in most instances.

### TUMORS OF PARATHYROID GLANDS

Tumors of the parathyroid glands are of two general types: (1) adenoma, the most common; and (2) carcinoma, which is extremely rare.

Adenomas are usually limited to one gland. Norris collected from the literature 322 cases of parathyroid adenoma with only 20 cases (6.2 per cent) having multiple tumors. The pathologic overactivity of these parathyroid tumors has already been discussed. However, there is no relation between the size and the functional activity of these tumors. The marked variation in location of these tumors, and the fact that they are usually single, often necessitates extensive surgical exploration to locate the tumor.

While several cases of carcinoma of the parathyroid glands have been reported, a careful analysis of the cases indicates a high percentage of wrong diagnoses. The malignant growth is associated with clinical manifestations of hyperparathyroidism.

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## 57

### Diseases of the Adrenal Cortex

George W. Thorn and Peter H. Forsham

Anatomy and Physiology of the Adrenal Cortex  
Functions of Adrenal Cortex  
Hormones of Adrenal Cortex  
Physiologic Activity of Adrenal Steroids  
Adrenal Cortical Hormone Preparations Available for Clinical Use  
Adrenal Cortical Hypofunction  
Primary  
Secondary  
Adrenal Cortical Hyperfunction  
Cushing's Syndrome  
Adrenal Virilism and Adrenogenital Syndrome  
Nonfunctioning Adrenal Cortical Tumor  
Clinical Picture  
Diagnosis  
Treatment

to the vital function of these organs. Shortly thereafter Brown-Séquard demonstrated that complete removal of both adrenals was followed promptly by death of the experimental animals. Later the studies of Abel and Takamine resulted in the isolation of epinephrine from the adrenal medulla. It was soon noted clinically, however, that epinephrine had little effect in the treatment of Addison's disease. From these observations and from experiments demonstrating that destruction of the medulla of both adrenals did not give rise to the classic signs and symptoms of adrenal insufficiency, it appeared that the life-maintaining substance liberated by the adrenal was derived from the cells of the cortex.

Thomas Addison's description in 1855 of a clinical syndrome which resulted from destruction of the adrenal glands first called attention

## ANATOMY AND PHYSIOLOGY OF THE ADRENAL CORTEX

The adrenal cortex consists of a narrow rim of cells surrounding the adrenal medulla. Arterial blood from the adrenal arteries and from small vessels arising from the renal and splanchnic arteries flows through sinusoids between columns of cortical cells into veins in the medulla whence all the blood leaves the adrenals by the adrenal vein. The cells secrete steroid hormones directly into the blood in the sinusoids. Cholesterol, present in high concentration in cortical tissue appears to be the precursor of the steroid hormones. From outside inward, three zones of cells may be distinguished: the zona glomerulosa, zona fasciculata, and zona reticularis. The zone of greatest hormonal secretion appears to be in the reticularis. The stimulus to both secretion and hyperplasia of the adrenal cortex is furnished by an anterior pituitary hormone, adrenocorticotrophin, or ACTH (see figure 104). This hormone

chloride and water loss, potassium retention, dehydration, circulatory failure, and death.

2. Regulation of water balance by opposing, directly or indirectly, posterior pituitary anti-diuretic hormone activity.

3. Regulatory effect on the quantities of carbohydrate, protein, and fat utilized in the catabolic pool. The adrenal hormones spare carbohydrate utilization while increasing that of protein and fat.

4. Regulation of the number of circulating eosinophils, lymphoid and thymus tissue, by promoting their lysis. Stimulation of polymorphonuclear neutrophilia.

5. The maintenance of certain androgenic functions such as axillary hair growth in women and nitrogen retention in both sexes.

6. The prevention of excessive melanin deposition in the pigment layers of the skin by a mechanism as yet unknown.

## HORMONES OF ADRENAL CORTEX

Approximately 26 steroids have been isolated from the adrenal cortex of hogs and cattle, of which only five have been demonstrated to be physiologically active. Most of the activity in the steroid fraction of the glands appears to be due to their content of 17-hydroxycorticosterone, or compound F of Kendall. The other cortical steroids in gland extracts probably represent in large measure precursors or degradation products of this steroid. Such substances include 17-hydroxy-11-dehydrocorticosterone (cortisone, compound E of Kendall), corticosterone (compound B), and possibly 11-dehydrocorticosterone (compound A) and 11-desoxycorticosterone (see figure 105). The last-named substance has been isolated, in very small quantities only, from adrenal extract. The first adrenal steroid to be partially synthesized was 11-desoxycorticosterone, in 1937. It was not until 10 years later that compound E (cortisone) was synthesized from bile acids by approximately 24 chemical steps.

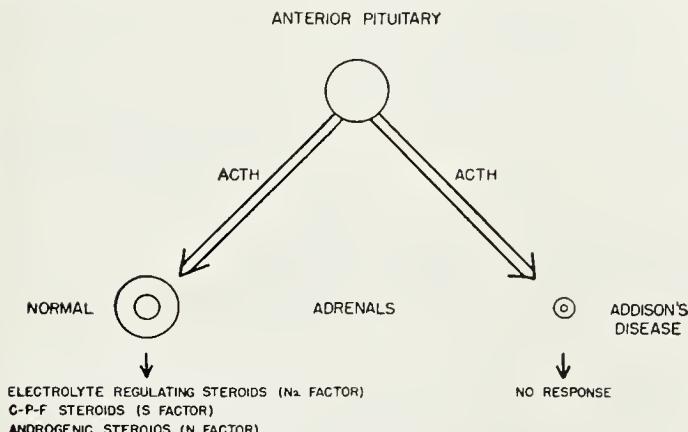


FIG. 104. Scheme of pituitary-adrenal relationship.

is secreted in response to stimulation by a humoral substance produced in the anterior hypothalamus under nervous control, or set off by epinephrine which in turn arises from the adrenal medulla following splanchnic stimulation. The pituitary-adrenal system is thus a functional unit, although medulla and cortex are of different embryologic origin.

## FUNCTIONS OF ADRENAL CORTEX

1. Regulation of the distribution and excretion of sodium, potassium, and chloride. Whereas excessive adrenal cortical hormone will lead to the retention of sodium, chloride, and water with a loss of potassium by kidneys and sweat glands, removal of the adrenals is followed by sodium

## PHYSIOLOGIC ACTIVITY OF ADRENAL STEROIDS

**Sodium and Chloride Retention.** Maximal activity is exhibited by 11-desoxycorticosterone, moderate activity by compounds A and B, and minimal activity by compound E (cortisone) and compound F (see figure 106).

THE RELATION OF CHEMICAL STRUCTURE TO  
SODIUM RETAINING AND CARBOHYDRATE REGULATING EFFECT

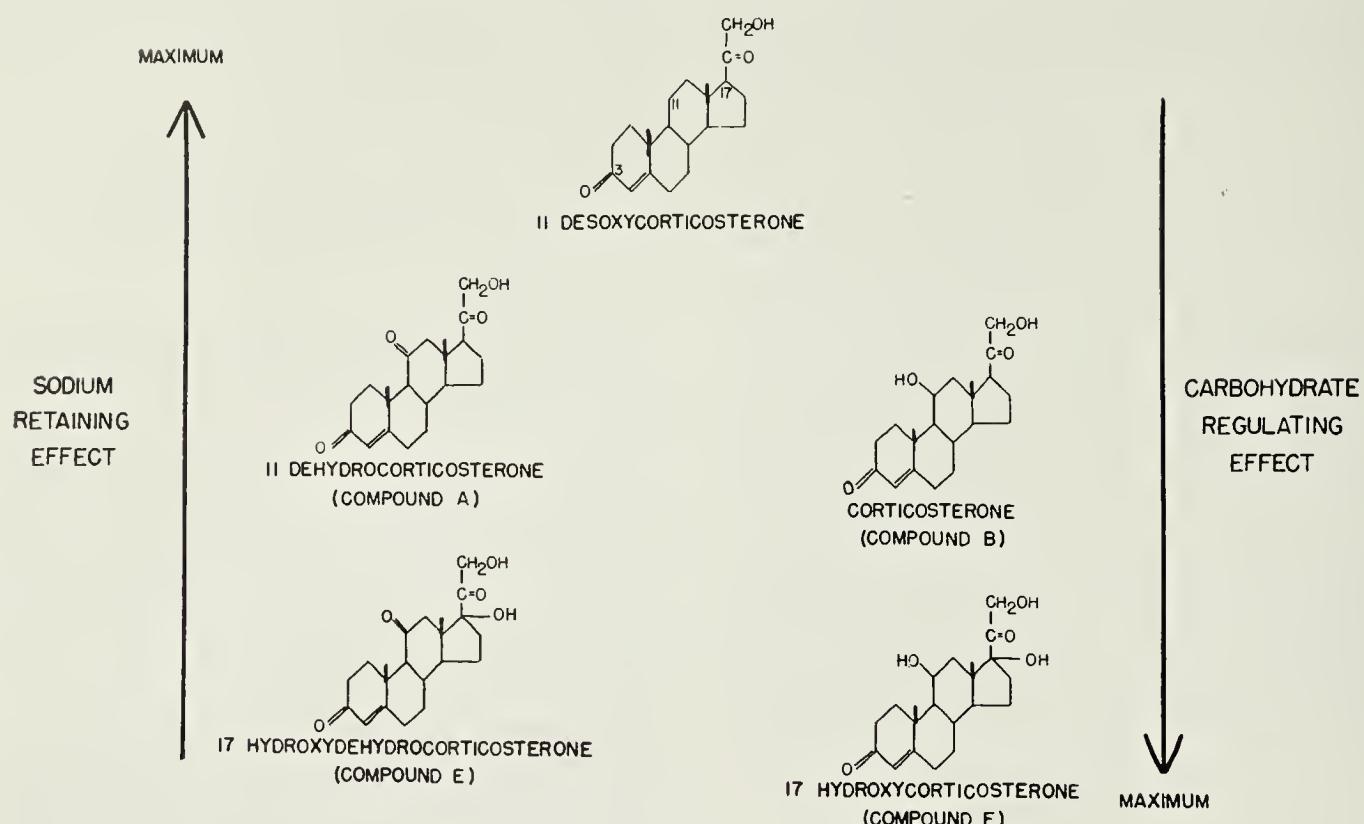


FIG. 105. Steroid formulas. (Courtesy, Thorn and Forsham: Metabolic changes in man following adrenal and pituitary hormone administration, in "Recent Progress in Hormone Research," vol. 4, New York, Academic Press, Inc.)

EFFECT OF ADRENAL STEROIDS ON URINARY Na AND K EXCRETION IN THE SAME PATIENT WITH ADDISON'S DISEASE ON CONSTANT DIET

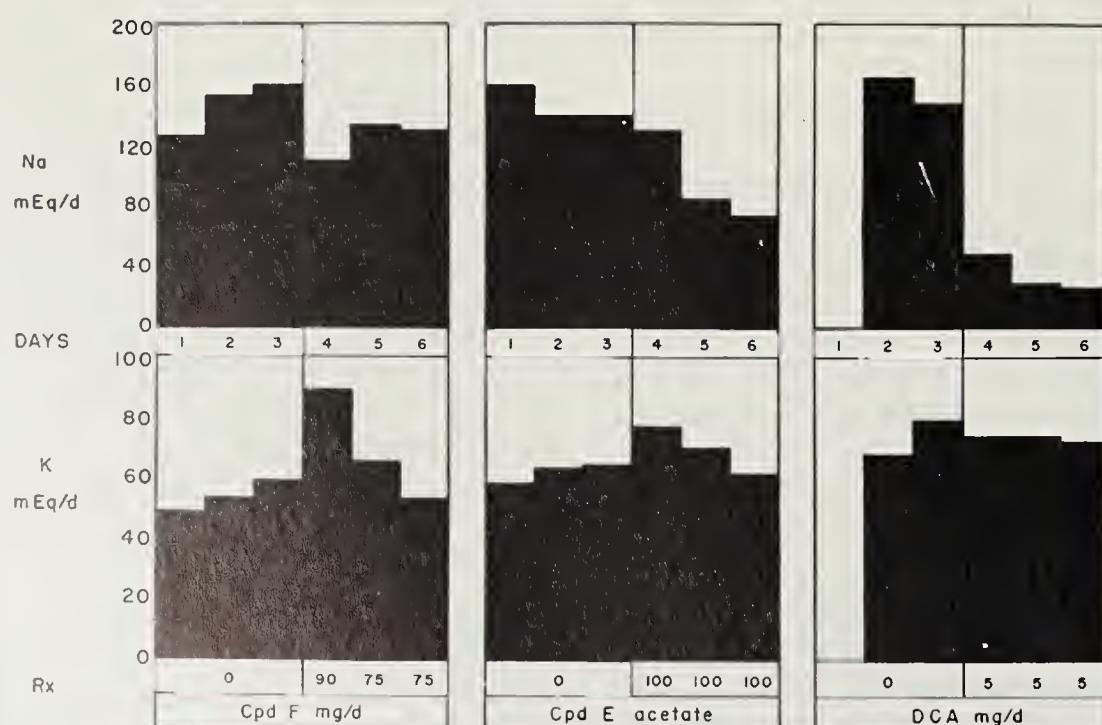


FIG. 106. Sodium retention.

**Potassium Excretion.** All adrenal steroids with physiologic activity increase the renal excretion of potassium. It appears that 11-desoxycorticosterone acts primarily on the renal tubular mechanism; whereas compounds E and F, in addition to affecting renal clearance of potassium, also increase potassium excretion as a consequence of increased protein breakdown and liberation of potassium. Compounds E and F quickly produce potassium retention, however, as increasing quantities of glycogen are laid down in the liver together with potassium.

**Water Metabolism.** All of the active adrenal steroids influence water metabolism indirectly through their effect on sodium, chloride, and potassium metabolism. Compound E and probably compound F appear to affect water balance directly by opposing the action of the posterior pituitary antidiuretic hormone.

**Conservation of Carbohydrate Stores.** The effect of adrenal steroids on the conservation of carbohydrate stores in the body may be ascribed almost exclusively to compounds E and F. This is achieved by increased mobilization and utilization of fat and by increased gluconeogenesis from protein (see figure 107).

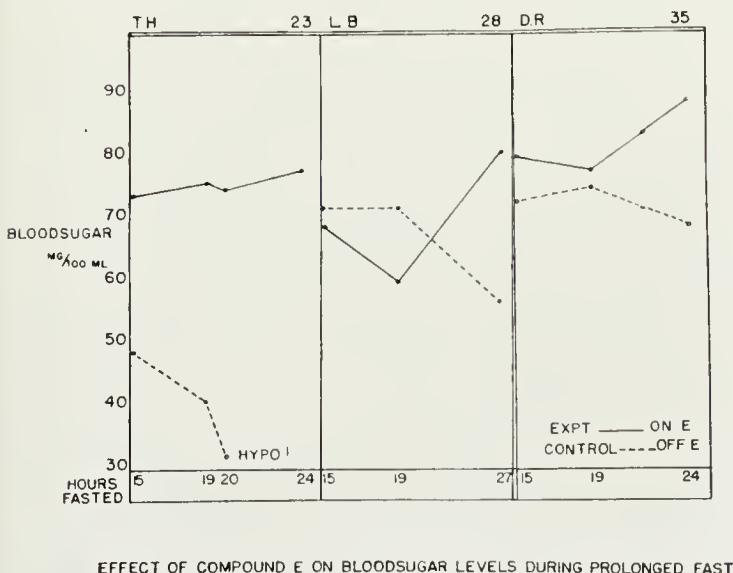


FIG. 107. All patients have moderate to severe Addison's disease.

**Partial Control of Leukocytes.** The partial control of leukocytes including the eosinophils, lymphocytes, and polymorphonuclear neutrophils, as well as thymus and lymphoid tissue, must be ascribed exclusively to the 11,17-oxygenated group of steroids—viz., compounds E and F.

**Adrenal Androgenic Function.** This function is best explained at present by the secretion of adrenal androgenic steroids related to adrenosterone. In part, however, it may be accounted for by degradation products of compounds E and F.

**Pigmentation.** None of the known pure steroids or extracts of the adrenal cortex has as yet been shown to decrease the melanin pigmentation associated with adrenal cortical insufficiency in man. The absence of pigmentation in cases of panhypopituitarism suggests that pituitary activity may be an important factor in modifying the pigmentation caused by adrenal cortical insufficiency.

**Conclusions.** It is now apparent that steroid compounds with an oxygen atom in the 11 and 17 positions in the cyclopentenophenanthrene ring show all the effects ascribed to adrenal cortical extracts; that steroids with an oxygen atom in the 11 position but none in the 17 position have lost the hematologic regulatory effect and much of the carbohydrate-regulating potency; and that the absence of an oxygen atom in the 11 position greatly increases sodium-retaining capacity at the expense of all other physiologic reactions.

The occasional dissociation of functional impairment found in adrenal insufficiency in man may be based in part upon the production of the several adrenal cortical hormones in variable quantities. Extreme salt deficiency is sometimes associated with little hypoglycemia; often marked hypoglycemia accompanies only minimal salt deficiency. In the rare instances of precocious puberty in boys or pseudohermaphroditism in girls due to androgenic replacement of the normal adrenal cortex, marked salt deficiency and pigmentation occur in conjunction with minimal carbohydrate deficiency and an excessive androgen formation (see Adrenal Virilism and Adrenogenital Syndrome, p. 602).

#### ADRENAL CORTICAL HORMONE PREPARATIONS AVAILABLE FOR CLINICAL USE

##### 1. Adrenal Cortical Extracts:

- a. Derived from beef adrenals, in aqueous solution, for intramuscular or intravenous use in 10 and 50 ml. vials. Such preparations must be administered every three to four hours for maximum effect,

the dose being from 5 to 20 ml. every three to four hours.

- b. Derived from hog adrenals, in sesame oil, for intramuscular use only, in 5 ml. vials. The dose is 1 to 3 ml. every six to eight hours.

Presumably these extracts contain all the naturally occurring, physiologically active adrenal steroids. These preparations, however, possess relatively little sodium-retaining capacity, and quantities up to 200 ml. of aqueous extract or 20 to 40 ml. of lipid extract may be given under conditions of stress without necessarily inducing excessive salt and water retention. In carbohydrate-regulating capacity the lipid extract is five to ten times as potent as the aqueous one.

### **2. Synthetic Compound E Acetate (Cortisone) :**

- a. A microcrystalline suspension in saline solution for intramuscular injection. One ml. contains 25 mg. of compound E acetate. The daily dose is 10 to 30 mg. in divided doses every 12 hours.
- b. Sterile cylindric pellets of crystalline material for subcutaneous implantation, 50 mg. per pellet. One such pellet will yield approximately 0.5 mg. of hormone a day. It is desirable to implant 10 to 20 such pellets for minimal daily maintenance.

Compound E must be supplemented with desoxycorticosterone acetate to afford satisfactory regulation of sodium and chloride metabolism in most patients.

Excessive doses of compound E (100 mg. or more daily), if continued, will lead to the development of Cushing's syndrome.

### **3. Synthetic Desoxycorticosterone Acetate (DCA) :**

- a. In sesame oil for intramuscular injection, 1 ml. contains 5 mg. of hormone; dose, 2 to 10 mg. daily.
- b. Sterile pellets (tablets) of crystalline material for subcutaneous implantation; 125 mg. pellets equivalent to the effect of 0.5 mg. of DCA in oil per day, or 75 mg. pellets equivalent to 0.3 mg. of DCA in oil per day.
- c. Sublingual tablets, 5 and 10 mg. of DCA

in inert vehicles; dose, one to two tablets every three to six hours.

Synthetic desoxycorticosterone acetate will need to be supplemented with compound E for satisfactory maintenance of most patients with severe Addison's disease. 11-Desoxycorticosterone acetate in excess (5 mg. or more daily) may give rise to toxic manifestations ranging from arthralgia to acute hypertensive cardiovascular episodes induced by excessive sodium and water retention.

## **ADRENAL CORTICAL HYPOFUNCTION PRIMARY**

### **ACUTE ADRENAL CORTICAL INSUFFICIENCY (ADRENAL CRISIS)**

This state is characterized by costovertebral angle pain, headache, lassitude, nausea, vomiting, diarrhea, hyperpyrexia, hypoglycemia, confusion, restlessness, circulatory collapse, coma, and death. This is often associated with pre-existing brown pigmentation of the skin and mucous membranes.

**Etiology.** Latent adrenal cortical insufficiency may be made acute by stress with its consequent increased requirement for cortical hormone. This may occur following major surgical operations, particularly if, in addition, adrenal cortical tissue is removed or destroyed; following traumatic injury to the back; or following hemorrhage. The latter is particularly likely to occur in the newborn at the time of delivery, or in the adult following heparin medication. Adrenal artery or venous thrombosis may give rise to a clinical picture indistinguishable from that of the acute surgical abdomen.

Severe, overwhelming infection, quite apart from contributing to acute adrenal cortical exhaustion, may involve the adrenal cortex and lead to its rapid parenchymatous or hemorrhagic destruction. This is especially likely to occur in the presence of meningococcemia or staphylococcemia. The earliest recorded instance of the association of fulminating purpura with bilateral adrenal hemorrhage appears to be that reported by Voelcker (1894). In 1911 Waterhouse summarized the available literature, collecting 15 cases and adding one of his own, and established a definite clinical syndrome. The second comprehensive review of the disease, now known as the

Waterhouse-Friderichsen syndrome, was prepared by Friderichsen in 1918.

**Diagnosis.** If, in the presence of a clinical picture suggestive of acute adrenal insufficiency, the level of circulating eosinophils is found *not to be* markedly depressed (less than 50 per cu. mm.), adrenal cortical insufficiency is likely, especially in the absence of an acute allergy which will tend to raise the eosinophil level. The Waterhouse-Friderichsen syndrome may be confused with the toxemia of any overwhelming infection. Without post-mortem examination it may be impossible to tell whether or not hemorrhages into the adrenal glands have occurred. The clinical evidence of widespread hemorrhagic manifestations and the sudden development of cyanosis and shock in a patient with septicemia who has made an initial satisfactory response to a specific chemotherapeutic or an antibiotic agent strongly suggest the possibility of complicating acute adrenal cortical deficiency.

**Treatment.** The aim of therapy is as follows: to provide sufficient fluid, plasma, whole blood, and sodium chloride solution to combat dehydration and shock; to correct and prevent hypoglycemia; to limit the spread of infection, when present, by specific chemotherapy.

1. Epinephrine hydrochloride (1: 1000 aqueous solution), 0.3 to 0.5 ml. subcutaneously if systolic blood pressure is below 80 mm. Hg.

2. Aqueous whole adrenal cortical extract, 20 to 50 ml. intravenously at once, and thereafter 10 ml. intramuscularly every hour for 12 hours, then every 2 hours for 12 hours, then every 4 hours for 12 hours, and finally every 6 hours until the patient has eaten well for 48 hours. "Lipo Adrenal Cortex" may be substituted for the aqueous extract, 1 ml. intramuscularly every 6 hours, or synthetic compound E (cortisone), 10 to 20 mg. intramuscularly every 2 to 3 hours.

3. Desoxycorticosterone acetate, 5 to 10 mg. in oil intramuscularly, given in two or more sites; thereafter, 5 mg. or less daily, depending on hydration, weight, and blood pressure.

4. On admission, 250 ml. of human plasma or concentrated human albumin; 50 Gm. is given intravenously with 30 ml. of aqueous adrenal cortical extract, 250 ml. of 10 per cent dextrose in saline, and 200,000 units of penicillin; the rate of infusion is 100 drops per minute or more. This may be repeated if the patient does not improve. Ten per cent dextrose in water is substituted for

saline solution after the blood pressure has become stabilized. Parenteral fluid should not exceed 3500 ml. in the first 24 hours of treatment. Fruit juices, milk, and soft solids should be started as soon as possible. Penicillin or other antibiotics should be continued prophylactically or as required to combat complicating infections (see Chapter 99). If nausea and vomiting require continued intravenous therapy, 1000 ml. of a solution containing 2 Gm. of dipotassium hydrogen phosphate, 0.4 Gm. of potassium dihydrogen phosphate, and 60 Gm. of glucose per liter should be used, with 500 ml. of 0.9 per cent sodium chloride.

With early signs of excess sodium retention (weight gain, pulmonary edema, anasarca, drowsiness, and hyperpyrexia), desoxycorticosterone is to be withheld, whole adrenal cortical extract or compound E substituted, potassium phosphate solution rather than sodium chloride solution administered, and the fluid intake limited to 1500 ml. a day.

#### CHRONIC ADRENAL CORTICAL INSUFFICIENCY (ADDISON'S DISEASE)

Adrenal insufficiency may manifest itself as a deficiency in the regulation of electrolytes, or in carbohydrate, protein, fat, or pigment metabolism. Deficiency of adrenal androgens may be observed particularly in postmenopausal females.

**History.** Between 1927 and 1930, Hartman, MacArthur, and Brownell; Rogoff and Stewart; and Swingle and Pfiffner described methods of preparing adrenal cortical extract capable of maintaining adrenalectomized animals over prolonged periods. The classic studies of Loeb and Harrop in 1933 demonstrated the beneficial effect of sodium salts in the treatment of patients with Addison's disease. Crystalline steroid compounds were recovered from adrenal extract by Kendall, Grollman, and Reichstein (1933-38). In 1937 Steiger and Reichstein synthesized desoxycorticosterone acetate. The availability of a crystalline adrenal steroid permitted the preparation of tablets or pellets of hormone for subcutaneous implantation with long-continued absorption (one year), thereby eliminating the necessity for daily injections of hormones. Later Kendall and Reichstein succeeded in accomplishing the difficult synthesis of adrenal steroids with an oxygen atom in the carbon-11 (Kendall's

compound A) and in the carbon-11 and -17 position (Kendall's compound E).

**Incidence.** True Addison's disease is a relatively rare disease, the incidence approximating 1 case per 100,000 of population. Undoubtedly many patients suffer from partial adrenal cortical insufficiency which may be revealed only under conditions of stress.

**Etiology.** Approximately 50 per cent of the cases show adrenal cortical atrophy, cause unknown. The remaining 50 per cent are due for the most part to partial or complete destruction of the gland by tuberculosis, rarely by neoplasm, amyloid disease, scleroderma, and hemochromatosis.

**Pathology.** In cases of primary adrenal cortical atrophy the gland is replaced largely by fat, only occasional small strands of residual cortical cells remaining. In tuberculosis of the adrenal gland, there is destruction of the cortex with partial replacement by caseous material leaving islets of active cortical tissue in many cases. In the rare cases of replacement by tumor, amyloid tissue, etc., the pathologic picture is that characteristic of the primary disease.

**Clinical Picture.** In order of frequency and occurrence one observes weakness, easy fatigability, weight loss, increased pigmentation, hypotension, small heart size, anorexia, nausea, vomiting and diarrhea, hypometabolism, nervous and mental irritability, and episodes suggestive of hypoglycemia (see table 56). The pigmentation

Table 56  
INCIDENCE OF SIGNS AND SYMPTOMS  
OF ADDISON'S DISEASE

Symptom	Incidence
Weakness and fatigability.....	100%
Weight loss.....	100%
Increasing pigmentation.....	94%
Anorexia, nausea.....	86%
Hypotension.....	54%

may present itself as a diffuse tanning with increased pigmentation over pressure points such as knees, elbows, and knuckles. There may be bluish black pigmentation of the mucous membranes and multiple black freckles over the body. Not infrequently vitiliginous areas or "leukoderma" may be noted. Addison's disease represents a severe form of adrenal cortical

insufficiency which is usually progressive and ends fatally unless adequate treatment is instituted. The chronic downhill course is usually accentuated by intercurrent crises.

**Diagnosis.** The diagnosis is suggested by the pigmentation, weight loss, and hypotension. In severe deficiency, hemoconcentration, low serum sodium and chloride, and a high serum potassium are observed. The finding of a serum Na mEq./K mEq. ratio of less than 30 is very helpful. The presence of genitourinary tuberculosis increases the probability of adrenal involvement.

In most patients a conclusive diagnosis is not possible without measurements of the functional capacity of the adrenal cortex.

**ACTH TEST.** A simple test for adrenal cortical competence consists in the intramuscular administration of 25 mg. of adrenocorticotrophin (ACTH) and the direct counting of circulating eosinophils immediately prior to and four hours

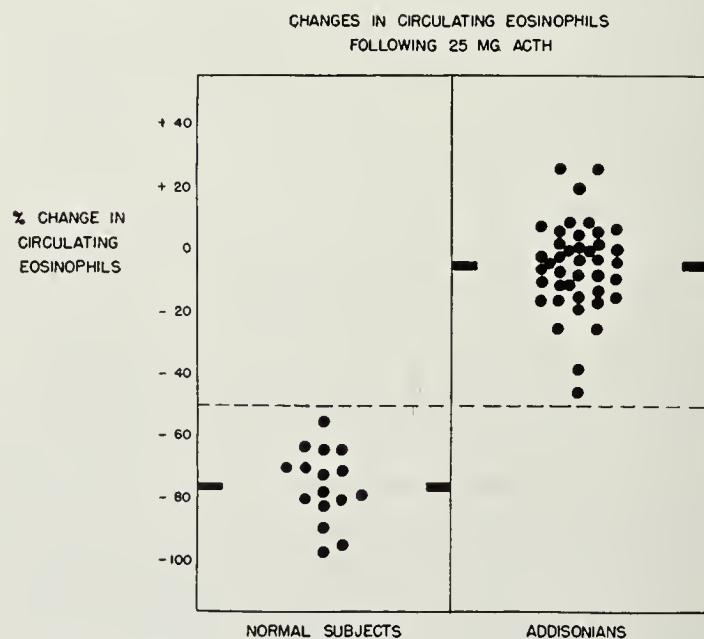


FIG. 108. The percentage change in circulating eosinophils as estimated four hours after the injection of ACTH. (Courtesy, Thorn and Forsham: Metabolic changes in man following adrenal and pituitary hormone administration, in "Recent Progress in Hormone Research," vol. 4, New York, Academic Press, Inc.)

after the injection (see figure 108). The technic is as follows:

**DIRECT EOSINOPHIL COUNT.** Blood treated with balanced oxalate<sup>1</sup> is drawn into an ordinary white

<sup>1</sup> Balanced oxalate to prevent coagulation of 5 ml. of blood consists of the residue after evaporation of 0.5 ml. of a solution containing 0.8 Gm. of potassium oxalate and 1.2 Gm. of ammonium oxalate per 100 ml. of water.

count pipet to the 0.5 ml. mark. The sample is diluted with an acetone-cosin diluting fluid in the usual manner employed for routine white counts. The pipet is shaken at once, without any delay, gently, exactly 50 times, and the contents are delivered into a special Fuchs-Rosenthal hemocytometer (0.2 mm. in depth). After waiting three minutes for adequate staining, four chambers are counted. The hypotonicity of the fluid causes blood cells to rupture, with the exception of the majority of the eosinophils. The granules of the latter take up the eosin and stand out as red spots, whereas debris and other cells are colorless. The average of four chamber counts multiplied by 6.25 yields the number of eosinophils per cubic millimeter (normal range 100 to 300). Certain precautions must be adhered to strictly in order to obtain satisfactory counts. Absolute cleanliness is essential, since eosinophils tend to cluster around foreign particles. The timing of the procedure must be followed closely, since eosinophils are unstable in the acetone-eosin diluent and tend to break down in the pipet after being in suspension for more than two minutes. The fluid must be filtered daily before use and kept in the icebox and made up fresh every two weeks. Occasionally the presence of yeast may interfere considerably with obtaining a clear delineation of the eosinophils. This is readily avoided by adding a few crystals of thymol to the balanced oxalate solution at the time of preparation. The diluting fluid consists of 5 ml. of acetone, 5 ml. of 2 per cent yellowish eosin (water and alcohol soluble), and 90 ml. of distilled water.

Another method is more convenient for capillary blood, since it allows for immediate dilution and storage in the diluted state without losing any of the eosinophils by lysis. The diluent consists of 50 mg. of phloxine, 50 ml. of propylene glycol, and 50 ml. of distilled water, and is stable indefinitely. With the use of this diluent the technic requires two minutes of hard shaking and a 15-minute wait for the dye to be taken up.

The activated secretions of the adrenal cortex (notably compounds E and F) depress circulating eosinophils by 50 per cent or more. If the fall does not exceed 50 per cent of the initial value (normally 100 to 300 eosinophils per cu. mm.), adrenal cortical insufficiency is highly probable. Additional assistance may be obtained by measuring the change in uric acid/creatinine ratio

two hours prior to and four hours following the ACTH test. In normal subjects an increase of 50 per cent or more is observed in uric acid/creatinine ratio following the administration of 25 mg. of ACTH, whereas patients with Addison's disease fail to respond (fig. 109).

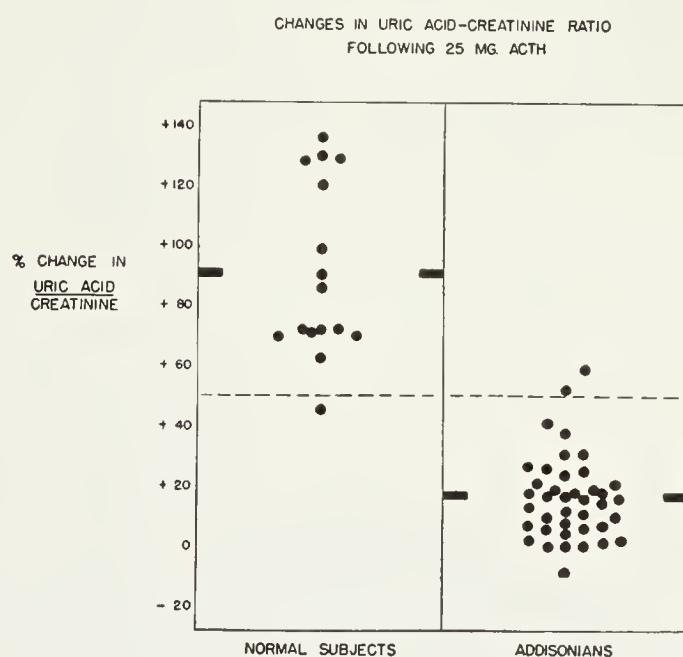


FIG. 109. The uric acid/creatinine ratio as computed on a two-hour specimen before ACTH and on a three-hour specimen, collection of which is begun one hour after ACTH.

**48-HOUR ACTH TEST.** This extension of the four-hour ACTH test is of especial value in patients in whom a more definitive diagnostic procedure is necessary. In this test, the excretion of the 17-ketosteroids under the influence of adrenal stimulation with ACTH is employed as a direct measure of adrenocortical reserve. Following the four-hour test, it is possible beginning at 4:00 P.M. to administer 10 mg. of ACTH every six hours for seven doses. The 24-hour urinary 17-ketosteroid excretion is determined on the day prior to the test and again during the second day of the test—i.e., from 24 to 48 hours. Normally, there occurs a rise of approximately 10 mg. in the ketosteroid excretion per 24 hours in males and 7 mg. in females.

**ANDROGENIC FUNCTION.** Androgenic function of the adrenal cortex may be evaluated by the estimation of the 24-hour urinary output of 17-ketosteroids, the normal values being 10 mg. in the female and 15 mg. in the male per day. In Addison's disease the average value for females is 1 to 3 mg. and for males 4 to 8 mg.

per day. Urinary corticoids representing the excretion of 11- and 11,17-oxysteroids may be measured and are found to be low in Addison's disease and greatly increased in Cushing's syndrome much as in normal subjects given pituitary adrenocorticotrophin.

**OTHER TESTS.** Further tests of adrenal cortical adequacy should include the measurement of capacity for prompt water diuresis, which is lost in adrenal insufficiency (Robinson-Kepler-Power water test: see table 57). Deficiency in salt metabolism may be demonstrated by showing the ability to withstand sodium chloride depletion (Cutler-Power-Wilder test: see table 58); and decreased glucostasis may be demonstrated by testing the capacity of a patient to survive a

24-hour fast (fig. 107). The application of the Cutler-Power-Wilder salt-withdrawal test and the 24-hour fast for hypoglycemic response should be carried out only in a hospital by competent observers after other tests have failed to provide a definitive answer, since these tests may precipitate adrenal crisis and death.

**Differential Diagnosis.** Addison's disease must be differentiated from the following conditions: neurasthenia (history and positive psychologic changes); chronic infections such as tuberculosis, brucellosis, etc. (bacteriologic and immunologic studies); chronic gastrointestinal disease (x-ray studies and stool cultures); thyrotoxic myopathy (basal metabolic rate, protein-bound iodine); hyperparathyroidism with its attendant weak-

Table 57  
ROBINSON-KEPLER-POWER WATER TEST  
(Modified for Convenience)

**PART I:** Withhold all fluids after 6 p.m.

Collect a night urine specimen, 10 p.m. to 7 a.m.

Give 20 ml. of water per kg. of body weight between 7:30 and 8 a.m., by mouth.

Collect hourly urine specimens, 8-9, 9-10, 10-11, 11-12 noon.

*Interpretation:* If the volume of any of the hourly specimens exceeds the total overnight volume, adrenal cortical insufficiency may be ruled out. If not, adrenal insufficiency may be present, but diseases such as nephritis, cirrhosis, and poor intestinal absorption associated with gastrointestinal disease may give a similar result.

**PART II:** Urea and chloride concentrations are obtained in an 8 a.m. blood specimen and in the overnight urine. The data thus obtained are fitted into an empiric equation which takes advantage of three abnormalities found in Addison's disease—decreased urea clearance, increased chloride clearance, and decreased water diuresis. A factor "A" is thus computed as follows:

$$A = \frac{\text{Urine urea nitrogen}}{\text{Plasma urea nitrogen}} \times \frac{\text{Fasting plasma chloride}}{\text{Urine chloride in night specimen}} \times \frac{\text{Volume of largest hourly day specimen}}{\text{Volume of night specimen}}$$

*Interpretation:* Addison's disease may be ruled out if A exceeds 30, and may be presumed to be present if A is less than 25. About 10 per cent false negatives are found when using both parts of the test.

Table 58  
CUTLER-POWER-WILDER TEST

**PROCEDURE:**

The patient is placed on a diet containing 1.5 Gm. or less of sodium chloride and approximately 4 Gm. or more of potassium a day. In addition, 1 ml. of 10 per cent potassium citrate per kg. of body weight is administered on the first and second day of the test, and 40 ml. of liquid per kg. of body weight is given. This procedure places the sodium-conserving mechanisms under considerable stress.

On the third morning of the test, 20 ml. of fluid per kg. of body weight is administered between 7 and 8 a.m., and a four-hour urine specimen is collected from 7 to 11 a.m.

Throughout, the patient's blood pressure, weight, and hematoerit must be followed frequently and the test must be discontinued whenever signs of adrenal insufficiency make their appearance.

**INTERPRETATION:**

Addison's disease may be excluded if the concentration of chloride in the four-hour urine specimen on the third day does not exceed 150 mg. % or 43 mEq. per liter, or if there has been no significant change in body weight, blood pressure, hematoerit, or clinical condition of the patient. It is advisable not to use the test in patients in whom adrenal insufficiency appears likely.

ness (changes in serum calcium, phosphorus, and alkaline phosphatase); myasthenia gravis (response to intramuscular neostigmine); islet-cell tumor with hypoglycemia (low fasting blood sugar level, resistance to insulin); "salt-losing nephritis" (presence of renal disease, absence of response to desoxycorticosterone acetate).

**Treatment.** Not infrequently patients are first seen in crisis, and the treatment is similar to that outlined under Acute Adrenal Cortical Insufficiency (see p. 593).

Interim treatment may be considered after a period of stabilization following the acute crisis.

**Interim Treatment.** Ideal substitution therapy consists of compound E acetate together with either a high sodium chloride intake (in excess of 10 Gm. per day) or supplementary desoxycorticosterone acetate. Whole adrenal cortical extract should be employed if compound E is not available, for, although many patients may appear to do well on DCA therapy alone, almost all will exhibit a decided clinical improvement when given supplementary compound E or whole adrenal cortical extract.

**COMPOUND E THERAPY: INTRAMUSCULAR INJECTIONS.** Patients are provided with an adequate caloric intake, and a total of 3 to 6 Gm. daily of enteric coated salt pills are given with meals. From 5 to 15 mg. of compound E acetate is injected intramuscularly twice daily (total daily dose 10 to 30 mg.). On such therapy patients will experience an increase in appetite, weight, strength, and clarity of thought accompanied by an improved electroencephalographic tracing. The weak sodium chloride-retaining activity of this preparation makes the use of supplementary DCA imperative in severe cases of adrenal insufficiency.

**SUBCUTANEOUS PELLETS OF COMPOUND E ACETATE.** After a month's trial on injected compound E, the patient may be given from 10 to 20 50 mg. pellets of compound E acetate. Although the amount of hormone derived from such pellets will not exceed 0.5 mg. per pellet per day, or 10 mg. for 20 pellets, the continuous absorption and sustained level of compound E apparently account for the physiologic effects observed, which are equivalent to the effects of at least twice the quantity of compound E acetate injected daily. The pellets are implanted under sterile conditions, using a special trochar and local anesthesia. The patient should receive 500 mg. of

ascorbic acid for two days preceding the implantation and for a week after in order to secure adequate wound healing. The pellets should be implanted about 1 inch away from the scar so as to prevent subsequent extrusion. The pellets are completely absorbed after four to six months, so that two or three implantations a year are necessary as a rule. No ill effects from overdosage have been encountered with this type of therapy, presumably because the quantities employed are subliminal. During times of stress additional substitution therapy must be provided in the form of daily injections of compound E or whole adrenal cortical extract and small amounts of DCA.

**WHOLE ADRENAL CORTICAL EXTRACT THERAPY.** The indications for the use of these extracts are the same as for compound E acetate. For maintenance, additional salt or DCA is usually necessary. Aqueous extract should be used in doses of 5 ml. three times a day, and lipoid extract in doses of 1 ml. three times a day. Much larger amounts may be used without any ill effect. In practice, whole adrenal cortical extract substitution therapy is indicated in the occasional case in which DCA leads to excessive sodium and water retention yet leaves the patient weak and tired.

**DESOXYCORTICOSTERONE ACETATE THERAPY.** Because of its almost exclusive action on salt and water retention, the use of DCA must be carried on with the dangers of overdosage constantly in mind, and this in turn requires careful "regulation" of the patient on therapy.

**DESOXYCORTICOSTERONE ACETATE IN OIL.** Daily basal weight, blood pressure, and hematocrit are determined in a patient on a moderately constant food intake, and, after obtaining a base line, 2 mg. of DCA in oil is given intramuscularly every day. This dose is increased every other day by 0.5 mg. of DCA in oil until the first signs of overhydration make their appearance—including weight gain, hemodilution, disappearance of wrinkles, and frank peripheral edema. The dose of DCA is then reduced by 0.5 mg. If the weight remains constant on this dosage, the patient is discharged and instructed to continue on this dosage. It should be noted that it is impossible in many patients to raise the blood pressure to normal levels without inducing some degree of edema, and that it is desirable to maintain the blood pressure at subnormal levels in most patients.

with Addison's disease rather than to overtreat with DCA.

In regulation, a lag of 48 hours in the ultimate DCA effect from a given dosage must be considered. In female patients the dose of DCA or supplementary sodium chloride may be reduced during the premenstrual period. In sensitive patients showing edema with as little as 1 mg. of DCA, whole adrenal cortical extract or compound E acetate therapy must be employed.

**SUBCUTANEOUS PELLETS OF DESOXYCORTICOSTERONE ACETATE.** Implantation of pellets should be considered only in patients who have been on daily injections for a matter of one or two months and who have been well regulated. For each 0.5 mg. of DCA in oil or 0.1 ml. of commercial DCA preparations, one 125 mg. pellet is implanted; for each 0.3 mg. of DCA in oil, one 75 mg. pellet is used. The former is implanted through a surgical incision (fig. 110), the latter with the aid of a

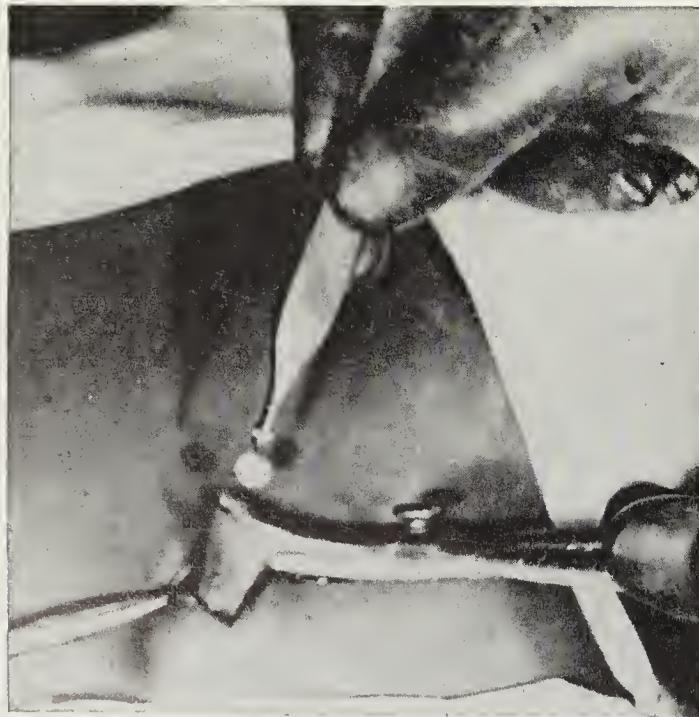


FIG. 110. The implantation of a 125 mg. pellet of desoxycorticosterone acetate through an incision in the lower back.

special trochar. The average patient will require from three to four pellets, which dissolve completely in approximately 9 to 12 months, at which time reimplantation should be undertaken. Whenever weight and blood pressure have remained well controlled, re-evaluation by the use of injected DCA need not be carried out, but this is very essential if such has not been the case.

The advantage of pellet therapy lies in the independence achieved by the patient on such therapy and in the fact that there is no lack of hormone at any time. On occasion, however, with stress and increased requirements, additional DCA may have to be given by injection (i.e., 5 to 10 mg. daily), and additional sodium chloride (3 to 6 Gm.) may also be required.

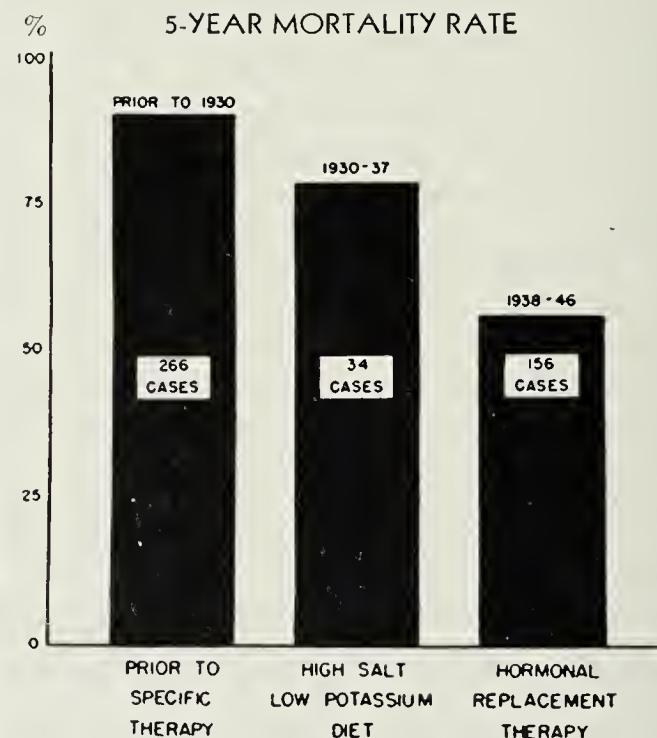


FIG. 111. Effect of hormone therapy on mortality rate in Addison's disease.

**UNDESIRABLE ACTIONS OF DESOXYCORTICOSTERONE ACETATE.** On occasion patients are sensitive to the oil used as a solvent for DCA. Allergic manifestations are characterized by local pain and induration at the site of injection as well as by myalgia and anorexia.

Manifestations resulting from excessive sodium and chloride retention comprise a group of signs and symptoms of increasing severity.

*Edema* usually appears early in treatment and is normally found soon after pellet implantation, but tends to disappear in most instances. Diuresis may be induced by restriction of salt in the diet and by the oral administration of 4 ml. of 20 per cent potassium citrate three or four times a day. The dose of DCA should be reduced. With the use of pellets, an attempt may be made to counteract some of the DCA effects by giving whole adrenal cortical extract or compound E acetate. As a final resort, pellets may have to be removed.

*Headache, hypertension, and cardiac enlargement* are further signs of excessive DCA therapy in the usual order of appearance. *Muscular weakness* with ascending paralysis is due to low serum potassium and is particularly amenable to treatment with potassium citrate. Rarely, cardiac standstill without demonstrable anatomic changes may occur. *Arthralgia* and *tendon contractures* often accompany somewhat excessive DCA therapy.

**Prognosis.** In the absence of active tuberculosis, the outlook is good with modern substitution therapy. On DCA therapy without compound E available, five-year survival in a large group of patients was increased from 5 per cent in the pre-salt treatment era to over 50 per cent (see figure 111). Further improvement is to be anticipated with compound E acetate available. In the presence of active tuberculosis, the outlook is less favorable, although there appears to be an unusual resistance to a spread of the disease in patients with adrenal insufficiency.

## SECONDARY

### ACUTE ADRENAL CORTICAL INSUFFICIENCY FOLLOWING POST-PARTUM PITUITARY NECROSIS

(See Simmonds' Disease, p. 552.)

**Clinical Picture.** The clinical picture is one of a pluriglandular deficiency with thyroid, gonadal, and adrenal cortical insufficiency. The latter is often characterized by a relatively *mild salt deficiency*, severe carbohydrate deficiency (spontaneous hypoglycemic episodes or inability to tolerate a fast), and *minimal* pigmentary changes. The basal metabolic level is depressed to levels between *minus* 20 and *minus* 40 per cent of normal, which is considerably lower than that seen in primary, uncomplicated Addison's disease. The 17-ketosteroid excretion approaches zero in both sexes.

**Diagnosis.** The diagnosis is made on the basis of the findings of adrenal cortical insufficiency in association with the signs of associated glandular deficiencies.

**Treatment.** The use of *whole adrenal cortical extract* or *compound E* is required, since such patients are not rehabilitated by desoxycorticosterone acetate alone. Thyroid medication must be administered with great care, since a severe crisis may be precipitated by elevating the basal

metabolic rate and thus increasing the demand for adrenal cortical hormone. It is advisable not to start thyroid before extract or compound E has been started. Then 15 mg. of thyroid may be used, and this may be doubled every two weeks until 60 to 100 mg. is being given. This dose should not usually be exceeded. In both males and females supplementary testosterone therapy is given to improve nitrogen retention and muscular development. A dose of 25 mg. of testosterone propionate twice weekly is given by injection, or 10 to 20 mg. daily of methyltestosterone by mouth, or as testosterone linguals.

### CHRONIC PANHYPOPITUITARISM WITH ACTH DEFICIENCY

(See Pituitary, p. 557.)

Pituitary hypoadrenocorticism may arise spontaneously and is characterized by adrenal insufficiency in the presence of other target gland deficiencies.

### ADRENAL CORTICAL HYPERFUNCTION

#### CUSHING'S SYNDROME

**History.** In 1932 Harvey Cushing described this syndrome associated with basophilic adenoma of the pituitary gland.

**Etiology.** The syndrome in all probability represents the effect of continued excessive secretion of adrenal cortical "carbohydrate-regulating" or "S" hormones (Albright). Presumably this may follow continued excessive adrenocorticotrophin (ACTH) liberation by a basophilic adenoma of the pituitary (Cushing's disease) or by primary hyperplasia or tumor of the adrenal cortex (Cushing's syndrome). There is general agreement that the physiologic changes encountered in Cushing's disease are the result of abnormal adrenal cortical hormone secretion and are not due to the action of ACTH itself.

**Incidence.** Cushing's syndrome is a relatively rare disease, most often observed in middle-aged individuals, being somewhat more frequent in women. ~~Basophilic adenomas~~ of the pituitary represent only 1 per cent of all pituitary tumors.

**Pathology.** There is usually diffuse or nodular hyperplasia of the adrenal cortex and hyalinization of some of the basophilic cells of the pituitary (Crooke's changes), not involving cells of

the basophilic adenoma if such be present. A unilateral adrenal cortical tumor is often associated with atrophy of the opposite gland. In the more prolonged or more severe cases there is generalized muscle wasting with fatty degeneration, par-

**Clinical Picture.** Patients with Cushing's disease present a characteristic appearance (see figure 112). There is adiposity confined to the face, neck, and trunk, the extremities being spared. A dorsal kyphosis in combination with the adipose,

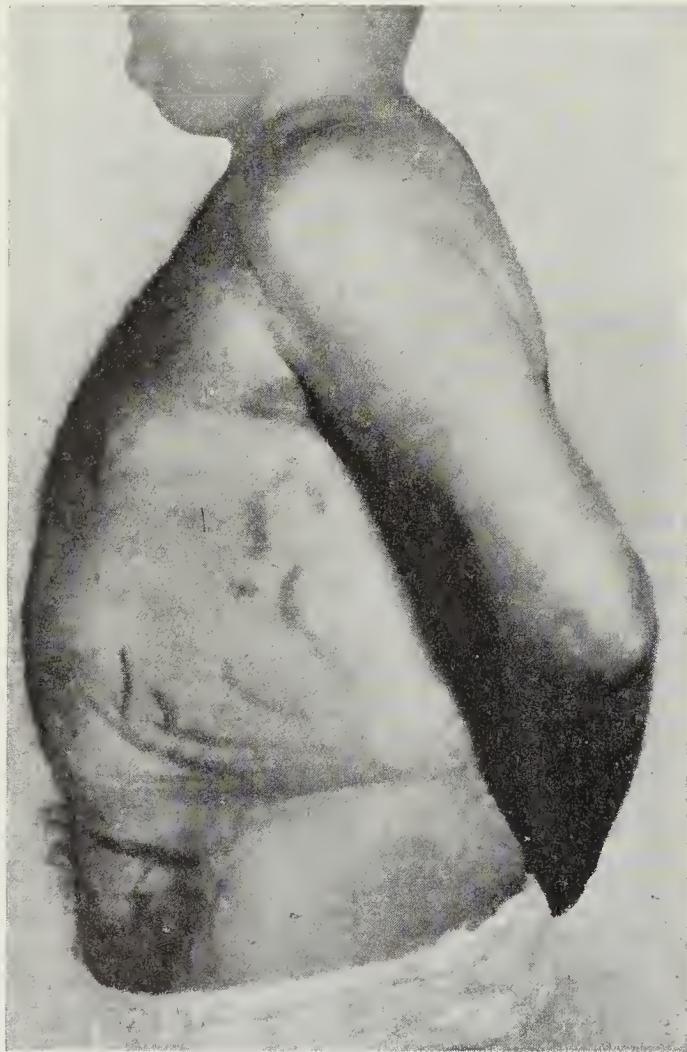


FIG. 112. A 26-year-old male with typical Cushing's syndrome. Note the bison neck and the deep red striae.

ticularly of the blood vessels. The pancreas often shows fatty necrosis.

**Pathologic Physiology.** Adrenal cortical hormones called forth spontaneously or by the excessive secretion of pituitary adrenocorticotropic hormone influence many body functions, including electrolyte balance, carbohydrate, fat, and protein regulation, and androgenic activity. Excessive secretion of the "S" hormones results in a depletion of body protein stores and abnormal carbohydrate and fat metabolism. One also may encounter excessive retention of salt and water associated with a low serum potassium and hypochloremic alkalosis. The presence of increased adrenal androgen production may shift the clinical picture toward that of adrenal virilism.



FIG. 113. Osteoporosis and compression fractures of lumbar vertebrae in the patient with Cushing's syndrome shown in figure 112. Note the typical fishbone deformity of the fractured vertebrae in the center.

plethoric facies and the fat pad in the interscapular area tend to give the patient the so-called "buffalo" appearance. The clinical picture varies in relation to the alteration in secretion of the several types of adrenal cortical hormone.

**SYMPTOMS DUE TO EXCESSIVE "S" HORMONE.** These include: "centripetal" fat distribution with obesity sparing the extremities; weakness and wasting of muscle; osteoporosis with dorsal kyphosis and often compression fractures of the vertebrae (see figure 113); marked thinning of the skin; purple striae over the abdomen, thighs, and upper arms; easy bruising with ecchymoses; poor wound healing with inadequate fibrous tissue replacement; diabetes, occasionally overt but more often latent; arteriosclerosis with systolic hyper-

tension, hypokalemia, hypochloremia, and high plasma carbon dioxide-combining power.

**SYMPTOMS DUE TO EXCESSIVE "SALT-RETAINING" HORMONE.** These include edema, hypernatremia, and hypertension.

**SYMPTOMS DUE TO INCREASED "N" HORMONE** comprising adrenal factors responsible for changes similar to those induced by male sex hormone. Increase in "N" hormone causes hirsutism, baldness, and acne without other evidence of masculinization, and amenorrhea or impotence.

**Diagnosis.** The combination of obesity, osteoporosis, weakness, hypertension, striae, and a diabetic tendency, together with a polymorphonuclear leukocytosis, lymphopenia, eosinophil count (direct) of less than 20 per cu. mm. (see table 59), with a urinary uric acid : creatinine ratio of

Table 59

**EOSINOPENIA OF CUSHING'S SYNDROME  
CONTRASTED WITH SIMPLE OBESITY**

Patient	Age	Eosinophils No./cu. mm.
<b>CUSHING'S SYNDROME</b>		
E. B., f.....	39	0
L. D., f.....	26	5
E. H., f.....	37	19
G. W., m.....	27	20
A. R., f.....	20	23
N. C., f.....	36	24
M. A., f.....	25	36
<b>SIMPLE OBESITY</b>		
R. M., f.....	42	606
T. S., f.....	18	550
F. S., f.....	34	530
L. H., m.....	14	280
E. G., f.....	53	300

0.8 or more and a diabetic blood sugar curve, suggests the diagnosis. Early in the disease, patients may fail to show osteoporosis, hypertension, or diabetes mellitus. The low eosinophil count differentiates Cushing's syndrome from simple obesity. An elevated urinary 11-oxysteroid with a normal or only slightly elevated urinary 17-ketosteroid excretion is suggestive. Intravenous and retrograde pyelograms should be made in an attempt to identify any suprarenal mass or adrenal cortical hyperplasia. X-ray of the sella turcica for tumor of the hypophysis will, as a rule, fail to reveal sellar enlargement with basophilic adenomas. X-rays of the retrosternal areas for thy-

mic tumor and pelvic examination for ovarian tumor should be carried out, since these coexist very occasionally with a classic Cushing's syndrome.

**Treatment.** Demonstration of an adrenal tumor demands immediate surgery with the precautions outlined below.

In the absence of demonstrable adrenal enlargement or in the presence of symmetric, bilateral enlargement ~~irradiation of the pituitary~~ *X-R* should be carried out prior to surgical exploration. In this form of treatment, 150 r daily with a 4500 r total is given through three portals over a two-week period. Response is judged by symptomatology, by an immediate and progressive fall in urinary uric acid: creatinine ratio, by a gradual slow rise in eosinophils beginning some four weeks after initiation of therapy, and by a fall in urinary 11-oxysteroid titer.

In the absence of any response to x-ray therapy within six weeks, it is wise to carry out a bilateral exploratory procedure. The lumbodorsal approach may be used in men; in females suspected of possible ovarian disease, a transabdominal approach may be preferable. The demonstration of an adrenal tumor is an indication for its removal, provided that adequate preoperative medication has been carried out. In the presence of bilateral hyperplasia a complete unilateral adrenalectomy, together with a contralateral partial adrenalectomy, is a useful but often dangerous procedure.

~~The management of a patient with Cushing's syndrome who undergoes surgery to the adrenals consists of:~~

1. The administration of 10 to 25 mg. of ACTH intramuscularly every six hours for at least four days preceding operation, and continuing up to one week after operation. This is done in an attempt to enlarge the adrenal opposite the one carrying a tumor, which is usually found to be atrophic, or to ensure the survival of the small portion of a hyperplastic gland left behind after subtotal adrenalectomy.

2. In the absence of an adequate response to ACTH preoperatively, or when ACTH is not used, whole adrenal cortical extract or compound E must be used in large quantities during, and especially after, operation. As much as 200 ml. of extract or 100 mg. of compound E per day may be required. Preceding operation and postoperatively, intravenous saline solution and 10 to 20

mg. of DCA intramuscularly should be administered. With the establishment of permanent adrenal insufficiency including pigmentation, which usually manifests itself within three weeks, therapy as outlined under Adrenal Cortical Hypofunction (p. 597) must be instituted.

3. A special effort should be made to promote wound healing, which is markedly slowed in Cushing's syndrome. To this end a high-protein diet, intravenous administration of albumin, and the daily administration of 25 mg. of testosterone propionate 10 days before and at least three weeks following operation are indicated. Ascorbic acid (200 mg. by mouth three times a day) will tend to improve fibrosis of the operative wound. The administration of 3 to 6 Gm. of enteric coated potassium chloride by mouth daily greatly enhances the establishment of a positive nitrogen balance and also allows for the use of mercurial diuretics in the event of excessive sodium and water retention, without further aggravating the hypokalemic alkalosis so characteristic of Cushing's syndrome.

#### ADRENAL VIRILISM AND ADRENOGENITAL SYNDROME

**History.** Apert, a French physician, introduced the term *adrenal virilism* in 1910 to designate masculinization in women related to alteration in adrenal cortical function. In rare instances adrenal tumors may be associated with feminization.

**Etiology.** An overproduction of steroid hormones with androgenic- or estrogenic-like activity arising from adrenal cortical hyperplasia or neoplasia may lead to a variety of clinical symptoms, depending upon the age and sex of the patient and the predominant type of steroid hormone. The condition is relatively uncommon but may occur from the prenatal state to the postmenopausal period.

**Pathology.** As yet there appears to be no correlation between the cytologic change in the adrenal cortex and the type of endocrine disturbance produced. The tumors are often highly malignant and metastasize chiefly to the liver and lungs.

**Clinical Picture.** Androgenic metaplasia of the adrenal cortex before birth is associated with pseudohermaphroditism in the female and pubertas precox with macrogenitosomia in the male. Signs of masculinization may vary considerably in degree, consisting of hirsutism, increased mas-

culinity, deepened voice, rapid growth, especially of the trunk, and male changes of external and internal genitalia. In the adult male, virilism usually goes unnoticed but is strikingly obvious in women. Pseudoprecocity in young females is characterized by enlargement of the clitoris, hirsutism without breast development, unusually rapid growth, and amenorrhea. This syndrome is most often due to adrenal cortical neoplasm. Concurrent activation of adrenal "S" hormone occurs on occasion and leads to obesity and such a syndrome as the "diabetes of bearded women" (Achard and Thiers). Diminished secretion of the salt factor occasionally leads to associated symptoms of Addison's disease in the younger age group. Estrogen-secreting tumors are extremely rare and are to be suspected in adult males with definite evidence of progressive feminization.

**Diagnosis.** Adrenal virilism is usually suspected from the history and physical examination. There is invariably an elevated excretion of urinary 17-ketosteroids. High values (50 mg. per day or more) with more than 50 per cent distribution in the so-called beta fraction in combination with a large amount of urinary estrogens are strongly suggestive of carcinoma of the adrenal as opposed to simple hyperplasia or adenoma of the adrenal cortex. In tumors associated with feminization one may expect a significant increase in excretion of estrogenic substances in the urine. In some instances a tumor in the adrenal region may be palpated. Changes in the pyelogram indicating displacement of the kidney are found more frequently.

Arrhenoblastoma of the ovary may lead to virilism similar to that seen in the adrenogenital syndrome, and, in the absence of localizing signs of tumor, exploration of both the adrenals and the pelvic region should be carried out. Rarer tumors are luteomas and lipid-cell tumors of the ovary. Tumors of the hypothalamus and pineal body may be difficult to diagnose, the virilism being due apparently to pressure on the hypothalamic area, stimulating pituitary gonadotrophin production. Macrogenitosomia precox due to pineal tumor appears to occur only in boys. Rare pineal tumors in girls do not appear to elicit similar manifestations. Tumors of the testes must, of course, be excluded in the male. In rare instances thymic tumors may be associated with the syndrome.

**Treatment.** Surgical removal of the tumor whenever possible is the procedure of choice. With unilateral adrenal tumors, it is highly desirable to administer pituitary adrenocorticotrophin for 48 hours prior to operation, with a view to increasing the functional activity of the otherwise hypoplastic uninvolved gland. During operation and immediately following, large quantities of aqueous adrenal cortical extract (50 to 200 ml.) intravenously and intramuscularly, or 50 to 200 mg. of compound E acetate intramuscularly, may be needed to prevent the development of acute adrenal insufficiency during the first 24 hours.

### NONFUNCTIONING ADRENAL CORTICAL TUMOR

The adrenal cortex may give rise to nonfunctioning tumors. These are composed of primitive adrenal cortical cells which do not appear to elaborate physiologically active steroids. These tumors are much rarer than the masculinizing tumors leading to the adrenogenital syndrome. Tumors of the adrenal stroma, such as sarcoma, are extremely rare. It is known that melan sarcomas of the adrenals are usually bilateral, but there is still a question as to whether these tumors actually originate in the adrenals. Carcinomas, of the breast and lung in particular, frequently metastasize into the adrenals. Metastatic adrenal carcinoma may induce the signs and symptoms of adrenal cortical insufficiency and occasionally results in death from this cause.

**Clinical Picture.** Replacement of functioning tissue may give rise to signs and symptoms of adrenal cortical insufficiency.

**Diagnosis.** Diagnosis may be made by pyelograms or exploration after careful preparation for possible adrenal crisis.

**Treatment.** Surgical removal of the tumor is the recommended treatment. Associated adrenal cortical insufficiency should be suspected prior to and following operation, and appropriate precautions should be taken (see p. 601).

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## Diseases of the Adrenal Medulla

George W. Thorn and Peter H. Forsham

Introduction  
Hyperfunction  
    Pheochromocytoma  
Nonfunctioning Tumors  
Clinical Picture  
Diagnosis  
Treatment

### INTRODUCTION

The adrenal medulla is part of the sympathetic nervous system. Phylogenetically, the cells of the adrenal medulla act as a ganglion to the pre-ganglionic, cholinergic fibers of the splanchnic nerves. The hormone of the adrenal medulla is composed of two fractions known as epinephrine and nor-epinephrine. The former has a central nervous stimulatory effect together with a vaso-dilatory action on peripheral blood vessels; the latter is devoid of any central nervous action and leads to constriction of small blood vessels and a consequent establishment of hypertension. No known disease due to hypofunction of the adrenal medulla has been shown to exist because of the compensatory action of the entire sympathetic nervous system. Hyperfunction of the adrenal medulla leads to an excess of its two hormones, epinephrine and nor-epinephrine, and the establishment of a syndrome characterized by paroxysmal episodes of hypertension and signs of excessive stimulation of the sympathetic nervous system.

### HYPERFUNCTION

#### PHEOCHROMOCYTOMA

**History.** Labb  , in 1922, first reported the phenomenon of intermittent paroxysmal hypertension associated with paraganglioma. In 1927 C. H. Mayo removed a palpable epinephrine-secreting tumor of the adrenal medulla, and relief of the hypertension followed.

**Etiology.** These tumors are derived from the chromaffin cells of the adrenal medulla or from extraadrenal chromaffin tissue, showing increased epinephrine secretion with signs and symptoms of hyperadrenalinism.

**Pathology.** The tumors are vascular, usually unilateral and encapsulated. In approximately 10

per cent of instances the tumors may be bilateral or located outside of the adrenal. In only one third of the cases are the tumors large enough to be palpated.

**Clinical Picture.** Two distinct syndromes occur:

1. Recurrent "attacks" of hypertension associated with signs of hyperadrenalinism—palpitation, headache, dizziness, sweating, weakness, anxiety, nausea, vomiting, diarrhea, dilated pupils with blurring of vision, paresthesia, circumoral pallor, a rapid pulse, and a rise in blood pressure which may attain a level of 300 mm. Hg or more. Death may result from cerebral hemorrhage, pulmonary edema, heart failure, and shock. A marked leukocytosis and transient glycosuria often accompany the attacks. There may be a variety of precipitating factors.

2. Persistent hypertension, indistinguishable from other types of benign or malignant hypertension.

**Diagnosis.** The intercurrent type may be suggested by the history and diagnosed by deliberately precipitating an attack by a change in position, pressure over the tumor, etc. With the diagnostic histamine test of Roth and Kvale a marked rise in blood pressure follows the intravenous injection of .025 to .050 mg. of histamine base. The persistent malignant type of hypertension associated with a pheochromocytoma may be discovered by employing the benzodioxane test in which 0.25 mg. per kilo body weight of this substance is administered intravenously over a period of two minutes. A sharp drop in blood pressure lasting from 2 to 10 minutes will occur if the hypertension is associated with excessive circulating epinephrine. The persistent type of hypertension associated with pheochromocytoma may be suggested by evidence of high cardiac output and marked spasm of the retinal vessels with little additional evidence of vascular disease. Precordial pain, tachycardia, and a rise in blood pressure may occur as side effects and restrict the use of this test substance somewhat.

**Treatment.** Early operative removal of tumors is the treatment of choice. Serious complications to be avoided are initiation of an attack of severe hypertension at the onset of operation, and acute epinephrine and adrenal cortical deficiency during and immediately following operation. Appropriate sedation and the use of adrenolytic preparations preoperatively should reduce the hazard of a cerebral vascular accident during the excitement stage of anesthesia. It may be necessary to administer large quantities (1 to 5 mg.) of epinephrine intravenously during the operation to prevent or correct hypotension, and epinephrine in oil may be useful postoperatively in gradually diminishing doses. It is also desirable to use large quantities of whole adrenal cortical extract (50 to 100 ml. of aqueous extract) during and immediately following operation.

### NONFUNCTIONING TUMORS

Nonfunctioning tumors of the adrenal medulla are quite common in early life but are encountered only rarely in adults.

*Neuroblastomas* arising from sympathetic nervous elements may develop in the adrenal medulla in children. These may be either benign fibril-containing ganglioneuromas or the highly malignant, more cellular sympathoblastomas.

**Clinical Picture.** Both lesions give rise to masses which are often palpable, reaching a large size unless treated early. Unlike sympathoblastomas, ganglioneuromas do not metastasize, and lead only to local pressure symptoms. Sympathoblastomas of the left adrenal tend to metastasize to the skull, giving rise to orbital growths and unilateral exophthalmos on occasion (Hutchi-

son's type); whereas metastases to the liver with massive hepatomegaly are more common when the primary focus lies in the right adrenal (Pepper's type). Lung and bone are frequently involved, and the metastases are often the first sign of the disease. Kidney invasion and hematuria are rare. Metaplasia to the more benign ganglioneuroma occurs on occasion.

**Diagnosis.** The clinical findings may be extended by intravenous and retrograde pyelograms which often show kidney displacement. Bone metastases are characterized by an uninvolved bony cortex with definite changes in the surrounding soft tissue seen by x-ray. Exploration usually furnishes the diagnosis.

**Treatment.** Early surgery with preoperative and postoperative x-ray therapy is the treatment of choice. Neuroblastomas are occasionally markedly radiosensitive. The outlook, while very poor in cases of sympathoblastoma, is not so unfavorable in the other types of tumor.

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## Diabetes Mellitus

George W. Thorn and Peter H. Forsham

Definition  
History  
Incidence  
Etiology  
Pathology  
Pathologic Physiology  
Clinical Picture  
Diagnosis  
Differential Diagnosis  
Treatment  
Complications  
Surgery and Diabetes Mellitus  
Diabetes Mellitus and Pregnancy  
Diabetes in Childhood  
Hemochromatosis

### DEFINITION

Diabetes mellitus is a chronic disorder in carbohydrate metabolism, resulting from a relative or absolute deficiency of insulin. The disease is characterized by hyperglycemia, glycosuria, and altered protein and fat metabolism which in turn may give rise to acidosis, dehydration, coma, and death.

### HISTORY

Diabetes is a disease which has been recognized from antiquity. Aretaeus described the disease and gave it the Greek name meaning "to run through a siphon." Chinese medical writings, as early as the seventh century, mentioned polyphagia, polydipsia, and polyuria. In the seventeenth century Willis described sweetness of the diabetic urine, "as if imbued with honey or sugar," and Helmont noted the presence of lipemia in a diabetic patient. In 1869 Langerhans described the islet cell formations in the pancreas which now bear his name. Von Mering and Minkowski carried out their classic experiments in 1889, in which they demonstrated that diabetes mellitus could be induced in dogs by extirpating the pancreas. In 1921, Banting, Best, and Macleod prepared an extract of pancreas capable of inducing a reduction in blood glucose level. Elimination of toxic substances and concentration of the principle, insulin, were accomplished by Collip working with this group. A great improvement in the regulation of diabetic patients followed Hagedorn's discovery in 1936

that the action of insulin could be prolonged by combining it with protamine.

### INCIDENCE

Diabetes mellitus is a disease of great importance due to its high incidence throughout the world and to the long period during which most patients require medical supervision. For example, it is estimated that within the United States there are approximately one million individuals with diabetes who may be expected to live an average of 20 years with the disease. Diabetes mellitus is characteristically a disease of late middle life, and hence the incidence of the disease rises rapidly with increasing age. It should be noted that, although 75 to 90 per cent of all diabetic deaths occur between the sixth and ninth decades, over 50 per cent of the patients develop diabetes prior to the age of 50 (Fig. 114). The high incidence of diabetes among females represents a sex difference which does not manifest itself until after the fourth decade. By the sixth decade the diabetic mortality rate for women is practically double that for men.

Although diabetes occurs among all races, the incidence among Jews is high. The disease appears to be infrequent among Chinese, Japanese, and East Indians, and to be mild when it does occur. The incidence of diabetes will be greatest in those areas in which the populace is composed of a high proportion of elderly individuals, a high proportion of Jews, or a high proportion of females, and in those communities in which obesity is frequent.

### ETIOLOGY

Despite years of careful study the exact mechanism which underlies the development of diabetes remains obscure in most instances. It is apparent, however, that a deficiency of insulin in relation to the body's need permits the disease to continue, since insulin therapy is followed by satisfactory regulation of the disease in most diabetic patients. Factors other than impaired insulin secretion ap-

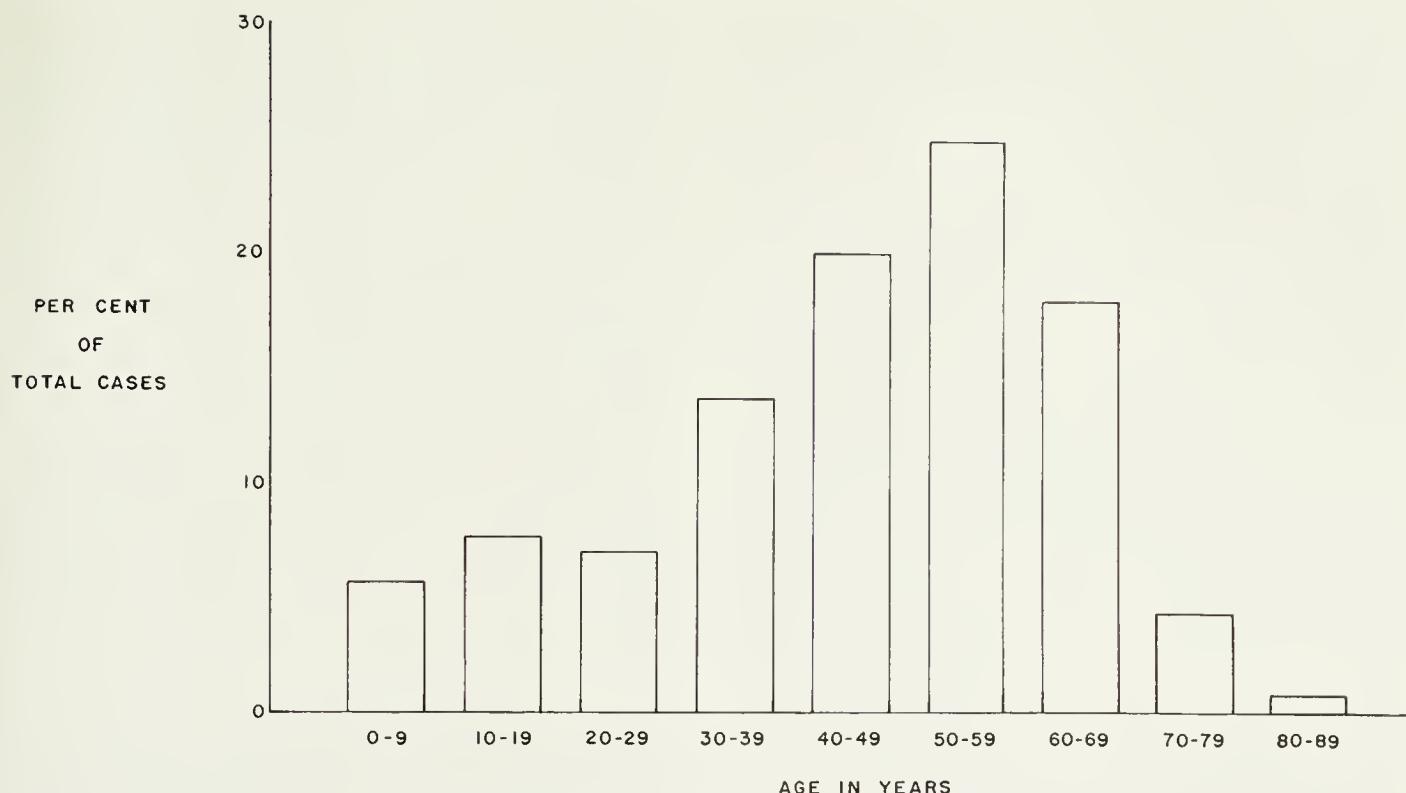


FIG. 114. The age of onset of diabetes mellitus.

pear to play an important role in the genesis of the disease. This is substantiated by the observation that minimal changes in islet cells occur in an appreciable number of classic cases of diabetes mellitus.

Three important etiologic factors appear to be *heredity, obesity, and hormonal disturbances*. It is now well established that the inheritance of the predisposition to develop diabetes follows a genetic pattern. In the past the importance of hereditary factors has been somewhat obscured by the failure to appreciate the fact that diabetes may develop in the offspring before it becomes manifest in the parent. Hence, in history taking, it is interesting to note that at the onset of diabetes 20 per cent of children have diabetic relatives, whereas 20 years later the incidence of diabetic relatives among the same group is 55 per cent. Obviously parents who succumb to other disease early in life may have masked their potentialities for developing diabetes. It appears probable that the predisposition to develop diabetes is inherited according to the Mendelian ratio for recessive characteristics (see Chapter 25). Thus the chances of a diabetic and a nondiabetic reproducing diabetes are minimal, although the immediate progeny may be carriers. If both parents are diabetic, the children will almost certainly inherit the disease. If neither marital partner has

diabetes, but if the disease has occurred in one of each of their parents, both marital partners must provisionally be considered to be carriers, and the chances are one in four that their progeny may in turn develop the disease.

The exact relationship between obesity and diabetes is not known, but the high coincidence of the two disorders is incontrovertible. It should not be inferred that all obese individuals develop diabetes. Actually the disease occurs in only a very small proportion of obese individuals, but the fact remains that diabetes selects 9 out of 10 of its victims from among the ranks of the obese. Leanness among adults confers a decreased susceptibility to the disease. Two provisional conclusions appear justified in relation to diabetes and obesity:

1. Relative insulin deficiency may be shown to be present in most obese individuals and is reversible by dieting and restoration to normal weight.
2. The continued demand for producing more insulin in the obese individual may well be an important factor in precipitating clinical manifestations of the disease in individuals with a predisposition to the development of diabetes.

Following the classic demonstration that pancreatectomy induced diabetes mellitus and that insulin therapy was effective in controlling the disease, it was thought that the severity of the

diabetic condition paralleled the impairment of insulin production. The concept that diabetes might result from a hormonal imbalance with either a relative or an absolute deficiency in insulin secretion is of recent origin. It appears possible that other endocrine glands may decrease the secretion of insulin, may compete with or inhibit its action, or may create within the organism a heightened level of metabolic activity which may in turn necessitate the secretion of more insulin than normal. The best known example is the aggravation of diabetes induced by excessive secretion of the anterior pituitary hormone with stimulation of the adrenal cortex and an increased output of adrenal cortical steroids. It is probable that anterior pituitary hormones other than adrenocorticotrophin play a direct role in the aggravation of the diabetic state, although the increased secretion of adrenal steroids appears to be the major factor.

It has been known for years that removal of the pituitary gland is followed by amelioration of the diabetic state, and it has been found more recently that adrenalectomy has a similar effect. Hyperthyroidism appears to aggravate diabetes primarily by increasing the total demand on the gland for increased insulin production by virtue of the large food intake, a heightened level of metabolic activity, and possibly an associated increase in adrenal cortical hormone secretion.

It is now possible to produce permanent diabetes by a variety of experimental procedures: (1) pancreatectomy; (2) administration of alloxan; (3) injection of anterior pituitary extract; and (4) administration of large quantities of glucose parenterally. In all instances in which permanent diabetes mellitus has been produced experimentally, degenerative changes in the beta cells of the islet tissue have been observed. Transient diabetes has been produced experimentally by the administration of purified pituitary adrenocorticotrophic hormone and certain adrenal steroids.

Infections are common in patients with diabetes mellitus. However, except in rare instances of extensive involvement of the pancreas with pancreatitis, it appears that the biologic role of acute infections in the genesis of diabetes is confined to unmasking potential diabetes and thereby precipitating the clinical manifestations of the disease. Infections may decrease glucose tolerance by (1) increased insulin antagonism resulting from increased elaboration of adrenal cortical hor-

mone in response to the stress; (2) increased insulin requirement resulting from fever, heightened metabolic level, dehydration, and acidosis; (3) possibly, decreased insulin production as a consequence of toxic parenchymatous changes in islet tissue.

Hemochromatosis, although rare, is a well-established cause of diabetes mellitus. In this disease large quantities of hemosiderin and hemofuscin are deposited in various body tissues, including the pancreas. Following the deposition of iron pigment there is secondary fibrosis and loss of functioning tissue. The disease affects males predominantly. Seventy-five per cent of patients with hemochromatosis may ultimately develop diabetes.

## PATHOLOGY

Following Opie's description in 1901 of hyalinization of the islets of Langerhans in patients dying from diabetes, it was hoped that a recognizable specific pathologic lesion had been found which would permit the diagnosis of diabetes mellitus to be made independently of the clinical record. Unfortunately, extensive studies indicate that the classic hyaline changes in islet cells occur in less than 50 per cent of patients with diabetes mellitus. It is true, however, that hyalinization of the islets is only rarely observed in patients other than diabetics. Fibrosis, hydropic degeneration, and lymphocytic infiltration of the pancreas may also occur in diabetic patients. With the exception of the relatively rare instances of acute and chronic pancreatitis and of hemochromatosis, the wide variety of pathologic changes observed in diabetics at post-mortem examination are secondary to the long-continued metabolic disturbance accompanying hyperglycemia, lipemia, and acidosis. Fatty infiltration and enlargement of the liver are common findings especially in diabetic children. Glycogen stores in the liver are usually depleted unless the patient has received insulin and carbohydrate immediately prior to death. In the kidney one may observe an accumulation of glycogen in the renal epithelium, especially in the loops of Henle. Advanced intercapillary glomerulosclerosis is seen frequently in patients with long-standing diabetes. The lesion is characterized by deposition of dense hyaline material in the glomeruli between the capillary loops and is most likely to occur in diabetics who have had the disease for many years. It is fre-

quently associated with a clinical picture characterized by hypertension, proteinuria, and edema (Kimmelstiel-Wilson syndrome). The loss of albumin in the urine may be great, often amounting to 5 to 20 Gm. daily.

Vascular lesions characterized by arteriosclerotic and atheromatous changes are the most important changes secondary to long-standing diabetes, and are responsible for the death of more than 50 per cent of patients who have had diabetes longer than 10 to 15 years. Changes occur predominantly in the coronary arteries, in the cerebral, retinal, renal, and pelvic vessels, and in the large vessels of the extremities. The vascular disease appears to progress more rapidly in poorly regulated diabetics, although its progressive manifestations in certain well-regulated diabetics are a cause for grave concern. It is not known at present why diabetic patients show arterial changes well advanced for their age. It has been assumed that this is secondary to the disordered fat metabolism and hypercholesterolemia associated with the disease.

### PATHOLOGIC PHYSIOLOGY

Evidence to date would indicate that, in all likelihood, diabetes mellitus develops as a consequence of disturbance in the balance between insulin production on the one hand and factors modifying its utilization on the other. A detailed analysis of the intermediate metabolism of carbohydrate is discussed in Chapter 30. The success with which most diabetic patients are treated with insulin, irrespective of cause or type of diabetes, indicates the important role which relative or absolute insulin deficiency plays in the pathogenesis of the disease. Insulin deficiency limits the efficient utilization of carbohydrate at normal blood levels. This is compensated for in part by a rise in blood sugar, the mechanisms involved apparently being increased carbohydrate formation (gluconeogenesis) and glycogenolysis.

In most patients, unfortunately, the elevation in blood sugar exceeds renal threshold, and the benefit derived by increased utilization of carbohydrate at the higher blood sugar levels is offset by the loss of carbohydrate in the urine. Hyperglycemia and glycosuria appear to stimulate mobilization of fat in the form of fatty acids and ketone bodies. These latter substances comprise a normal source of energy but, in the presence of impaired glucose utilization, may be formed in

excess of the capacity of the tissues to utilize them. A rising blood ketone level is followed by ketonuria. Because of the highly acidic nature of the ketone bodies it is necessary for the kidney to excrete fixed base with the ketone acids.

In unregulated diabetes the body loses glucose, ketone bodies, fixed base, and water. Dehydration resulting from the loss of fixed base and water further impairs the utilization of glucose and increases the insulin requirement, thus aggravating the already serious insulin deficit. With increasing ketosis and dehydration, coma may supervene. Since insulin is not believed to exert a direct effect upon carbohydrate utilization by nervous tissue, coma must in all probability be due to the direct effect of acidosis and dehydration on the central nervous system and vascular system.

Until recently the probable mechanism by which insulin acts has remained a mystery. The stimulating studies of Cori and Cori (1946), however, indicate that there is a substance present in high concentration in the anterior pituitary gland which may be shown to be capable, *in vitro*, of inhibiting the action of hexokinase in its role of catalyzing the phosphorylation of glucose to glucose-6-phosphate at the expense of adenosine triphosphate (ATP). Insulin, which apparently is without effect upon hexokinase itself, effectively blocks this inhibition, whereas certain adrenal cortical extracts enhance it. Since most of the important biologic fates of glucose appear to proceed by way of an initial hexokinase-catalyzed phosphorylation, it might be predicted that insulin deficiency or an excess of anterior pituitary or adrenal hormones might inhibit hexokinase unduly and thus effectively decrease glucose utilization. Conversely, an excess of insulin might be expected to overcome the inhibition of hexokinase, and glucose might then be phosphorylated at a normal rate. Excellent examples of this type of antagonism are found in the diabetes associated with Cushing's syndrome and acromegaly on the one hand, and with the increased insulin sensitivity observed in patients with Addison's disease and Simmonds' cachexia on the other.

Recent evidence suggests that insulin might exert an inhibiting effect on phosphatase activity, which has been shown experimentally to be increased in the liver of diabetic animals. The ultimate result of such an inhibition would be to increase the quantity of phosphorylated glucose

carried in the blood. Another point at which insulin may affect carbohydrate metabolism is suggested by Levine in his studies on the increased rate at which glucose can be transferred across cell membranes in the presence of insulin.

### CLINICAL PICTURE

Patients with well-established diabetes mellitus complain of general weakness, loss of body weight, excessive appetite, thirst, and polyuria. Frequently there is pruritus, especially about the genitalia, often complicated by secondary infection. Impotency in the male and amenorrhea in the female are frequent in long-standing or more severe cases. In its early stage the disease may be asymptomatic. In more advanced cases, in addition to evidence of weight loss, one may find degenerative changes such as *cataracts*, *diabetic retinosis*, generalized *arteriosclerosis*, *infections*, and *gangrene* involving the feet and toes. The first evidence of severe diabetes may be in the form of coma, usually precipitated by infection (table 60). The cheeks are flushed and the clinical signs of acidosis, dehydration, and coma are present, viz.: reduced intraocular tension, dry skin and mucous membranes, low blood pressure, hypothermia, rapid pulse, acetone breath, air hunger or Kussmaul respirations, and abdominal tenderness.

In children and young adults the disease may develop rapidly and be more severe. There is less correlation in children between obesity and the

onset of diabetes mellitus than is found in adults. In general, the greater the age at onset of diabetes, the less severe the disease, and certainly in obese individuals past 50 the course of diabetes mellitus is usually mild. Certain patients with obesity and mild diabetes lose all evidence of the disease when reduced to ideal weight. Some believe that this type of diabetes may differ in quality from the more severe types. Diabetes associated with Cushing's syndrome may be mild but at the same time relatively insulin resistant. This is also true of patients with acromegaly and diabetes.

Very frequently one of the complications of diabetes mellitus first prompts the patient to seek medical care, and the underlying metabolic disorder is then discovered. Common complaints are pain, coldness and gangrene of extremities, change in vision, repeated infections such as carbuncles and furuncles, and neuropathies.

### DIAGNOSIS

The diagnosis of diabetes mellitus will on occasion be suggested by the history. In most instances, however, the discovery of glycosuria in a routine urine specimen will initiate a careful search for other evidence of the disease. Glycosuria is most likely to be present immediately following a meal. Glycosuria alone is not conclusive evidence of the presence of diabetes mellitus. *Glycosuria associated with ketonuria is almost always pathognomonic of diabetes mellitus.* The final diag-

Table 60  
DIFFERENTIAL DIAGNOSIS

	<i>Hypoglycemia</i>	<i>Diabetic Coma</i>
History.....	Insufficient food; excess insulin; excess exercise	Insufficient insulin; infection; gastrointestinal upset
Onset.....	Following <i>short-acting insulin</i> : Suddenly, a few hours after injection Following <i>long-acting insulin</i> : Relatively slower, many hours after injection	Gradually, over many hours
Course.....	Anxiety; sweating; hunger; headache; diplopia; incoordination; twitching; convulsions; coma. (Headache, nausea and haziness especially following long-acting insulin)	Polyuria; polydipsia; anorexia; nausea; vomiting; labored deep breathing; weakness; drowsiness; possibly fever and abdominal pain; coma
Physical findings.....	Pale, moist skin; full, rapid pulse; dilated pupils; normal breathing; B.P. normal or elevated; overactive reflexes; positive Babinski sign	Florid, dry skin; Kussmaul breathing with acetone odor; decreased B.P.; weak, rapid pulse; soft eyeballs
Laboratory findings....	Second urine specimen sugar- and ketone-free; low blood sugar; normal serum CO <sub>2</sub>	Urine contains sugar and ketone bodies; high blood sugar; low serum CO <sub>2</sub>

nosis, however, should be made only after demonstrating a high fasting blood sugar level (over 150 mg. %) or impaired glucose tolerance. In either event, the laboratory tests should be repeated before the final diagnosis is established. By definition, diabetes mellitus is a metabolic disorder characterized by a disturbance in carbohydrate metabolism, and the diagnosis must be established by appropriate chemical methods (see Chapter 87).

**Fasting Blood Sugar.** The range of normal for the true blood sugar level taken in the fasting postabsorptive state is approximately 70 to 110 mg. per 100 ml. of whole blood. With a value above 150 mg. %, under fasting conditions, a presumptive diagnosis of diabetes mellitus may be made. It is essential, however, to confirm this observation by repeated analyses.

A simple but effective "screening test" consists in the determination of the blood glucose level on a single sample of blood taken three hours after the ingestion of a breakfast containing approximately 100 Gm. of carbohydrate, as detailed in table 61. A value within normal limits at this time excludes diabetes mellitus.

Table 61  
100 GM. CARBOHYDRATE BREAKFAST

Food	Quantity	Carbohydrate (Gm.)
Orange juice.....	8 oz.	24
Cooked cereal..... or	4 oz.	16
Dry cereal.....	1 oz.	
Bread.....	2 slices	32
Egg.....	1	..
Butter.....	2 pats	..
Milk.....	6 oz.	9
Cream.....	3 oz.	4
Sugar.....	3 tsp.	15
Coffee and tea.....	ad lib.	..
		100

**Glucose Tolerance Tests.** A patient should be properly prepared for a glucose tolerance test by the administration of at least 300 Gm. of carbohydrate daily for two to three days prior to the test. This averts abnormalities in the tolerance curve which might occur as a consequence of a decreased carbohydrate tolerance due to starvation, or a diet of low carbohydrate content. In

the test, blood glucose levels are determined in conjunction with the administration of a measured quantity of glucose. At appropriate intervals during the test, the urine is examined for the presence of sugar.

**Oral Glucose Tolerance Test.** A sample of urine and one of whole blood are obtained from the patient in the fasting state. The patient is then given 100 Gm. of glucose dissolved in 500 ml. of water and flavored with lemon juice. Samples of urine and whole blood are taken for determination of glucose one-half, one, two, and three hours after the ingestion of the glucose.

**INTERPRETATION.** The fasting level for glucose is normally below 120 mg. %. The maximum level in normal subjects properly prepared in advance is 150 mg. %, and this usually occurs in a specimen taken at the end of the first hour. The blood glucose level should return to or below the normal fasting level by the end of three hours (fig. 115). Abnormally high levels of blood glucose attained during the first hour of the test, with a rapid fall to normal values or flat curves with no appreciable rise, reflect primary alterations in rate of glucose absorption (thyroid disorders, sprue, etc.).

**One-Hour, Two-Dose Oral Glucose Tolerance Test (Exton and Rose's Test).** In this test use is made of the Staub-Traugott effect for the diagnosis of early diabetes mellitus. This effect consists of the failure of a moderate amount of glucose to raise the blood sugar of a normal subject if this dose is administered within an hour after giving a similar amount of glucose previously. This test has the practical advantage of requiring only one hour. The technic consists in the oral administration of 50 Gm. of glucose in 400 ml. of lemon-flavored water to a fasting subject after drawing a sample of venous blood for a blood sugar determination. One-half hour later another 50 Gm. of glucose is administered similarly, and one-half hour after that another blood sugar sample is drawn.

A normal response will include a fasting blood sugar level below 120 mg. %, a half-hour level not exceeding 160 mg. %, and a one-hour level below the half-hour one. The urine should be examined for glucose. Diabetes mellitus is suggested by a blood sugar level which exceeds 160 mg. % one-half hour after the second dose of glucose, or if the blood sugar level at the end of one hour exceeds the half-hour value.

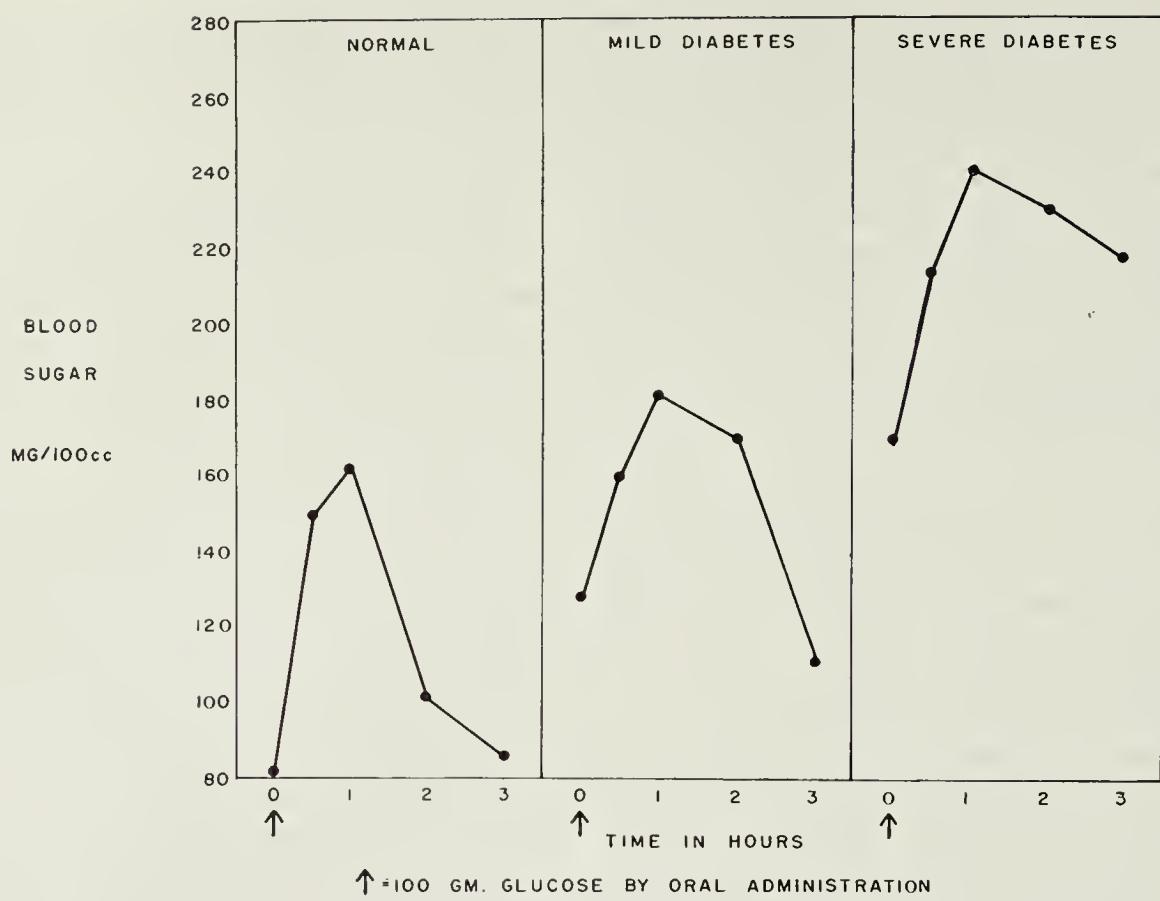


FIG. 115. Oral glucose tolerance curves.

**Intravenous Glucose Tolerance Test.** Under certain circumstances it is desirable to study the glucose utilization without reference to gastrointestinal absorption. Glucose may be given intravenously in a dose of 0.5 Gm. per kg. of body weight in an aqueous solution containing approximately 20 Gm. of glucose per 100 ml. of pyrogen-

free distilled water. It is administered by intravenous infusion, regulated to a constant rate, such that the total volume is given in one-half hour. Samples of urine and whole blood are collected 30, 60, 90, and 150 minutes after the intravenous infusion is begun. The fasting blood sugar level is normally re-established in 90 minutes.

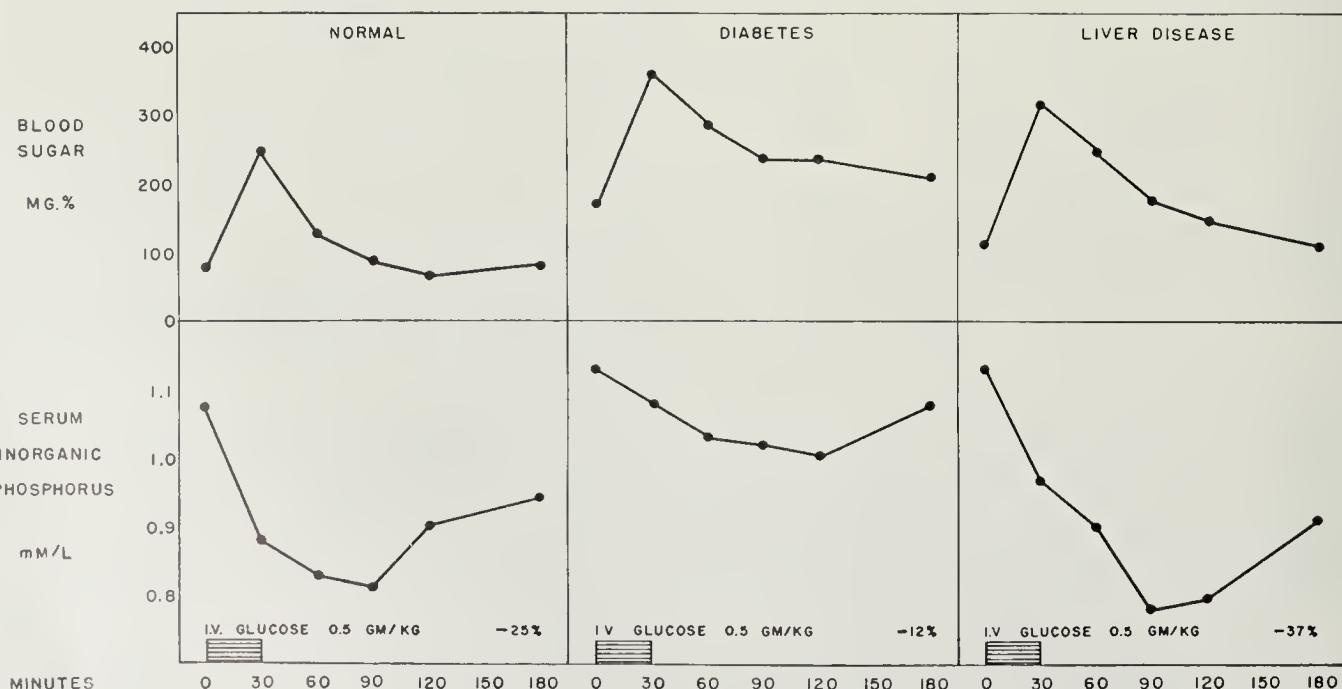


FIG. 116. Characteristic changes in serum inorganic phosphorus during the intravenous glucose tolerance test.

Occasionally hyperglycemia and glycosuria will be noted with the glucose tolerance test in patients with liver disease. Presumably the ability to store glucose as glycogen is impaired. Hence a greater than normal quantity of glucose circulates temporarily in the blood stream. The differential diagnosis between this condition and the impaired glucose utilization of diabetes may be made by a study of the changes in serum inorganic phosphorus level during the glucose test. It is well known that in the presence of adequate insulin the utilization of glucose is associated with a transient withdrawal of inorganic phosphorus from the blood serum (fig. 116).

Following intravenous glucose (0.5 Gm. per kg. of body weight) given over a 30-minute period, normal individuals will show a drop of approximately 30 per cent in serum inorganic phosphorus during the course of the test. Patients with liver disease and a high glucose curve, but without diabetes, will show a normal fall in serum inorganic phosphorus (30 per cent of initial level); whereas patients with true diabetes mellitus who fail to use glucose at a normal rate show a less than 15 per cent fall.

### DIFFERENTIAL DIAGNOSIS

**Melituria:** PERSISTENT MELITURIA will most often be found to be glycosuria, and a manifestation of diabetes mellitus. Persistent glycosuria also occurs in the presence of a lowered renal threshold. This may be present in otherwise normal subjects, in pregnancy, and in patients with chronic renal disease. In all of these situations glucose disappears from the urine as the blood sugar level approaches 100 mg. %. True renal glycosuria is a rare familial abnormality *in which glucose is present in all specimens of urine*, including those passed after an overnight fast. The condition is not prediabetic.

*Transient glycosuria* may occur frequently in nondiabetics under conditions of stress or following the ingestion of a high-carbohydrate meal (alimentary glycosuria). Under such conditions, the fasting blood sugar and the glucose tolerance values will be normal.

**MELITURIA OTHER THAN GLYCOSURIA.** Lactose is found in the urine of lactating women but not, as a rule, in appreciable quantities during the course of pregnancy. Sugars other than glucose may be found in the urine following the ingestion of large quantities of fruit (levulosuria).

Pentosuria and levulosuria also occur as inborn errors of carbohydrate metabolism.

Increased intracranial pressure due to cerebral tumor, brain trauma, or arterial hypertension may on occasion give rise to glycosuria and hyperglycemia. It is often difficult to differentiate the hyperglycemia and glycosuria associated with these conditions from true diabetes mellitus. The presence of ketonuria with an adequate dietary intake strongly points to diabetes mellitus. In these cases signs and symptoms of intracranial disease suggest the true diagnosis. In most instances of this type the disturbance in carbohydrate metabolism disappears with improvement in the cerebral disorder. In elderly diabetic patients with advanced cerebral vascular disease one may, of course, encounter a combination of both conditions. A negative history of diabetes prior to the onset of the intracranial disease is extremely helpful.

Since Cushing's syndrome and acromegaly are frequently complicated by diabetes mellitus, it is essential to keep these diseases in mind when evaluating the cause of diabetes mellitus in a new patient. Hyperthyroidism, in addition to increasing the rate of intestinal absorption of glucose, thus giving a transient hyperglycemia with the oral glucose tolerance test, may on occasion be a factor responsible for precipitating diabetes mellitus in a patient so disposed. Since correction of the thyrotoxicosis exerts a beneficial effect upon the course of diabetes mellitus, it is essential to keep the possibility of this complication well in mind.

**Coma.** A critical and difficult differential diagnosis presents itself in patients with glycosuria and coma (see table 60).

With a cerebro-vascular accident and glycosuria, it is unusual to observe ketonuria unless the patient has not eaten for a considerable period. The carbon dioxide-combining power is usually normal and dehydration may be absent. The reflexes may be asymmetric and the blood pressure normal or elevated. Since diabetics under treatment may be admitted in coma, it is essential to differentiate between a hypoglycemic reaction and diabetic coma. Sugar may be found in the first urine specimen of a patient in insulin shock, although it will be absent later. The blood sugar is low, and the carbon dioxide-combining power is normal. The onset may be sudden in patients on crystalline insulin treatment, or very gradual if pro-

tamine insulin is used. Headache is a common prodromal manifestation of excessive protamine insulin administration. The skin is moist in insulin reaction, in contrast to the dehydrated skin of diabetic acidosis. Breathing is normal, as is the odor of the breath, in contrast to Kussmaul's type of breathing and an acetone odor of the breath in diabetic acidosis. The reflexes are overactive in hypoglycemic reaction, with dilatation of the pupils. (The differential diagnosis of coma is considered in some detail in Chapter 8.)

### TREATMENT

The aims of diabetic management are: (1) the correction of the underlying metabolic abnormalities by dietary management or supplementary insulin therapy, or both; (2) the attainment and maintenance of ideal body weight; and (3) the prevention of complications commonly associated with the disease. In the treatment of a patient with diabetes mellitus, the physician has an excellent opportunity to accomplish and maintain complete rehabilitation. Successful therapy will depend upon the thoroughness with which the physician understands the particular problems in each individual case and upon how conscientiously the patient coöperates. Because there is so much for both patient and physician to learn at the outset, it is wise to consider seriously the advantages of hospitalization for 7 to 10 days for initial study and instruction.

In approaching the treatment of a patient with diabetes mellitus, it is essential to be certain at the outset that there is no active focus of infection anywhere in the body. Infections of the urinary tract, gallbladder, teeth, and sinuses should be looked for particularly, and a chest x-ray is a requisite. It is also desirable to obtain a careful evaluation of the state of the cardiovascular system.

### DIET

The arrangement of diet and insulin therapy is not difficult if a few basic facts are obtained and appreciated. Thus the keystone in treatment is the establishment of a patient's ideal weight. Every effort should be made to attain this as rapidly as is feasible. The difference between the patient's actual weight and his ideal weight immediately establishes the *total caloric intake*. Thus, an adult patient above ideal weight will need less than a maintenance diet. Adult patients

should receive at least 1 to 1.5 Gm. of *protein* per kg. of body weight, and children at least 2 to 3 Gm. per kg. of body weight. Authorities vary greatly in the quantity of *carbohydrate* which they recommend. All agree, however, that it is essential for a diabetic patient to utilize at least 100 Gm. of carbohydrate daily if ketonuria and acidosis are to be prevented. A diet of 175 to 250 Gm. of carbohydrate is adequate for most adults. Men doing heavy labor may require 300 to 400 Gm., as will growing children.

The quantity of *fat* permitted in the diet is limited to that necessary to complete the caloric requirement. In obese adult patients the quantity of fat will be small in view of the low total caloric intake i.e., 15 to 20 calories per kg. of body weight. It may be relatively large in undernourished patients, in children, and in men who perform hard labor (30 to 40 calories per kg.). For example:

Patient's ideal weight 150 lb. (68 kg.)

Patient's actual weight 190 lb. (86 kg.)

It is estimated that patient should be restricted to  $86 \times 18 = 1548$  calories daily for weight reduction

$\text{Protein} = 1.5 \times (\text{ideal weight } 68 \text{ kg.})$

$= 102 \text{ Gm.} = 408 \text{ calories}$

$\text{Carbohydrate} = 200 \text{ Gm.} = 800 \text{ calories}$

$1208 \text{ calories}$

$\text{Fat} = 1548 \text{ calories} - 1208 = 340 \text{ calories};$

$34\% = 38 \text{ Gm. of fat}$

i.e., Diet = protein, 102 Gm.; carbohydrate, 200 Gm.; fat, 38 Gm.

Distribution of carbohydrate:

$\frac{2}{7}$  at breakfast

$\frac{2}{7}$  at lunch

$\frac{2}{7}$  at dinner

$\frac{1}{7}$  before retiring

In converting the above diet prescription to a satisfactory or convenient menu, it is necessary to indicate both the type of food and the distribution of the diet throughout the day. For practical purposes, this is done by first apportioning the carbohydrate. It is apparent that diabetic regulation will be simpler with a greater number of feedings involving small quantities of carbohydrate, rather than with infrequent meals containing large quantities of carbohydrate. Such dietary regulation minimizes peaks in the daily blood sugar curve.

The number of meals will depend upon a pa-

tient's habits and his opportunities for eating. It is desirable, in so far as is possible, to encourage a patient to lead a normal life. Most patients will experience no difficulty in arranging three regular meals and a late evening feeding. In the case of children or adults at home, it may be possible to provide supplementary nourishment at 10:30 a.m. and 4 p.m. The distribution of the quantity of food in the diet will also vary with the type of insulin employed. This will be discussed in more detail under Insulin Therapy, page 616. As a first approximation, carbohydrate may be divided as follows:  $\frac{2}{7}$  at breakfast,  $\frac{2}{7}$  at noon,  $\frac{2}{7}$  with an evening meal, and  $\frac{1}{7}$  as a late evening feeding. It is customary to apportion fat and protein in

approximately the same manner. The degree of coöperation and effectiveness obtained in dietary management will parallel the patient's understanding of basic dietary principles. Simplicity in apportioning the calories is essential. The diet should minimize unnatural concern for nonessential details. In tables 62-65, food equivalents are presented in a simplified form as suggested by Caso and Stare. Utilizing these tables, it is relatively simple for a patient to substitute one equivalent for another and thereby obtain variety as well as relative accuracy in dietary management. A diet adapted to the individual's food habits will have a much better chance of being followed. It is desirable to ingest a well-rounded diet to ensure

Table 62  
FOOD EQUIVALENTS\*

**LIST 1.** Protein Equivalents—Negligible Carbohydrate, 7 Gm. Protein, 5 Gm. Fat.

Meat, fish, poultry .....	1 oz. (28 Gm.)	Sardines.....	3 medium
Egg .....	1	Salmon, tuna, crabmeat.....	$\frac{1}{4}$ cup
Cheese, American .....	1 oz. (28 Gm.)	Peanut butter.....	$1\frac{1}{2}$ tbs.
Cheese, cottage.....	2 tbs.	"Cold meat".....	3 thin slices
Oysters, clams, shrimp.....	5	Frankfurter.....	1 average size

**LIST 2.** Vegetables—Negligible Carbohydrate, Protein, and Fat.

Celery	Lettuce
Cucumber	Radishes

**LIST 3.** Vegetables—7 Gm. Carbohydrate, 2 Gm. Protein, Negligible Fat. (1 serving equals  $\frac{1}{2}$  cup.)

Asparagus	Carrots	Onions
Beans, string	"Greens" (beet, chard, dandelion,	Squash
Beets	mustard, kale,	Tomato
Broccoli	spinach, turnip)	Turnip
Cabbage		

**LIST 4.** Fruits—10 Gm. Carbohydrate, Negligible Protein, Negligible Fat.

Apple, $\frac{1}{2}$ medium	Orange, 1 medium or $\frac{1}{2}$ cup juice
Applesauce, unsweetened, $\frac{1}{2}$ cup scant	Peach, 1 medium
Banana, $\frac{1}{2}$ small	Pear, $\frac{1}{2}$ large
Berries: Raspberries, blueberries, or blackberries, $\frac{1}{2}$ cup	Pineapple, fresh, diced, $\frac{1}{2}$ cup
Cantaloupe, $\frac{1}{3}$ medium	Pineapple juice, unsweetened, $\frac{1}{3}$ cup
Cherries, 12 small	Plums, 2 medium
Dates, 2 small	Prunes, 2 medium
Grapefruit, $\frac{1}{2}$ medium	Strawberries, 12 large
Grapefruit juice, unsweetened, $\frac{1}{2}$ cup	Tangerine, 1 large
Grapes, 12 medium	Watermelon, 1 small slice with rind, $\frac{1}{3}$ lb. (151 Gm.)

**LIST 5.** Carbohydrate Equivalents—16 Gm. Carbohydrate, 3 Gm. Protein, Negligible Fat.

Beans, baked and lima, $\frac{1}{4}$ cup	Soda crackers, 5
Bread, baker's, 1 slice	Peas, $\frac{1}{2}$ cup, scant
Corn, $\frac{1}{4}$ cup (1 small ear)	Potato, white, 1 small (size, 5 to 1 lb., 454 Gm.)
Rice, macaroni, noodles, $\frac{1}{2}$ cup	Cereals, cooked, $\frac{1}{2}$ cup
Graham crackers, 2	Cereals, dry, flakes, 1 cup

**LIST 6.** Fat Equivalents—Negligible Carbohydrate, Negligible Protein, 4 Gm. Fat.

Butter or fortified oleomargarine, 1 tsp.	Oil, 1 tsp.
Cream, light, 2 tbs.	Bacon, 1 slice, long, crisp
Mayonnaise, 1 tsp.	Milk (1 cup, 8 oz.), 12 Gm. carbohydrate, 8 Gm. protein, 10 Gm. fat

\* From E. K. Caso and F. J. Stare: Simplified method for calculating diabetic diets, *J.A.M.A.*, 133:169, 1947.

*Table 63*  
SUMMARY OF COMPOSITION OF FOOD EQUIVALENTS\*

<i>Foods and Equivalents</i>	<i>Carbohydrate (Gm.)</i>	<i>Protein (Gm.)</i>	<i>Fat (Gm.)</i>
Milk, 1 cup.....	12	8	10
Protein equivalents, List 1.....	0	7	5
Vegetables, List 2.....	0	0	0
Vegetables, List 3.....	7	2	0
Fruits, List 4.....	10	0	0
Carbohydrate equivalents, List 5.....	16	3	0
Fat equivalents, List 6.....	0	0	4

\* From E. K. Caso and F. J. Stare: Simplified method for calculating diabetic diets, *J.A.M.A.*, 133:169, 1947.

*Table 64*  
CONVERSION OF DIET PRESCRIPTION TO DIETARY MENU  
A DIABETIC DIET ORDER

	<i>Amount</i>	<i>C (Gm.)</i>	<i>P (Gm.)</i>	<i>F (Gm.)</i>
Milk, skimmed.....	4 cups	48	32	0
Protein equivalents, List 1.....	6 servings	0	42	30
Vegetables, List 2.....	As desired	0	0	0
Vegetables, List 3.....	2 servings	14	4	0
Fruits, List 4.....	3 servings	30	0	0
<i>Total</i> .....	..	92	78	30
Carbohydrate equivalents, List 5.....	7 servings	112	21	0
Fat or equivalents.....	2 servings	0	0	8
<i>Total</i> .....	..	204	99	38

Carbohydrate (C), 200 Gm.; protein (P), 102 Gm.; fat (F), 38 Gm.; calories 1600.

an adequate intake of the essential vitamins and minerals. A vitamin supplement, particularly vitamins of the B-complex group, is desirable for most diabetic patients and essential for those on a reduced caloric intake. Under the latter circumstance, the need for supplementary calcium and iron should also be considered.

### INSULIN THERAPY

**Insulin Regulation.** Most diabetic patients will require insulin. A few will not need insulin, particularly during periods on a reduction diet. Failure to maintain a normal fasting blood sugar level under dietary management represents a definite indication for the use of supplementary insulin therapy, as does the presence of ketonemia or ketonuria.

There are three general types of insulin which one may employ:

1. Crystalline insulin, with a relatively short period of maximum action (four to six hours).

2. Protamine zinc insulin, with a prolonged period of maximum action (30 hours).

3. Modified insulin, such as globin insulin with zinc and combinations of protamine zinc and crystalline insulin, with an intermediate period of action (18 to 20 hours). (See table 66.)

In the case of uncomplicated diabetes the patient should be put on an appropriate diet and insulin therapy started at once. As a rule, mild, middle-aged diabetics will do well on protamine zinc insulin alone, whereas the severe and younger diabetics usually require both crystalline and protamine zinc insulin or one of the modified insulins with an intermediate period of action.

The insulin dosage will be established in one of three ways: (1) In mild diabetics one may start arbitrarily with 10 units of protamine zinc insulin daily and increase this dose by 5 units daily until the urinary sugar has been reduced to zero in the overnight fasting state. In general, it is not wise to exceed a daily dose of 50 units of protamine

*Table 65*  
SAMPLE DAY'S MENU

The carbohydrate in these meals is divided on the basis of  $\frac{3}{4}$  at breakfast,  $\frac{2}{3}$  at lunch,  $\frac{2}{3}$  at dinner, and  $\frac{1}{4}$  in an evening feeding.

#### BREAKFAST

Grapefruit,  $\frac{1}{2}$   
Soft-cooked egg, 1  
Oatmeal,  $\frac{1}{2}$  cup  
Whole wheat toast, 1 slice  
Butter or oleomargarine, 1 tsp.  
Milk, 1 cup, skimmed  
Coffee

#### LUNCH

American cheese, 1 oz. (28 Gm.)  
Bread, 2 slices  
Fat, 1 tsp.  
Tomato salad  
Prunes, 2  
Milk, 1 cup, skimmed  
Tea

#### DINNER

Roast leg of lamb, 4 oz. (113 Gm.)  
Carrots,  $\frac{1}{2}$  cup  
Mixed green salad  
Small potato, 1  
Bread, white or enriched, 1 slice  
Orange slices  
Milk, 1 cup, skimmed  
Coffee

#### EVENING FEEDING

Milk, 1 cup, skimmed, and 2 graham crackers

zinc insulin. (2) One may administer 10 to 20 units of crystalline insulin preceding each meal as long as the premeal urine specimen reveals more than 1 plus sugar. Having established the total

It should be appreciated that the therapeutic effect of a standard dose of protamine zinc insulin is not attained until the second or third day of continued administration. (3) A third method of initiating insulin therapy is to estimate the 24-hour urine sugar on a standard diet and to administer 1 unit of insulin for every 2 Gm. of urine sugar found. This may be given as protamine zinc insulin in a single dose or crystalline insulin in divided doses throughout the day.

Young diabetics require relatively large quantities of insulin for adequate control, in contrast to elderly diabetics. Patients with complicating liver disease present a special problem since these individuals are unable to store glucose satisfactorily as liver glycogen. Consequently, they tend to display postprandial hyperglycemia and easily develop hypoglycemia with insulin therapy.

In initiating insulin therapy for diabetic management, it is essential for the patient to be able to test his urine for reducing substances and for ketone bodies. It is of great assistance in establishing the adequacy of diet and insulin therapy for a patient to keep a daily chart in which the urine is checked prior to breakfast, lunch, dinner, and retiring (table 67). Consideration of the periods during the 24 hours in which the patient displays glycosuria or ketonuria will permit accurate readjustment of insulin dosage and dietary intake.

**Insulin Reactions.** Patients must be instructed concerning insulin reactions. Crystalline insulin given in excess produces a rapid and characteristic reaction associated with hunger, sweating, palpitation, and tachycardia. Patients are usually well aware of these early symptoms and are immediately and completely relieved by the ingestion of carbohydrate. Protamine zinc insulin, on the other hand, causes a gradual reduction in blood sugar and is more frequently associated with headache. In most instances protamine zinc insulin reactions occur during sleep or in the morning (see table 60). Often, particularly in elderly patients with hypertensive cerebral vascular disease, the headache associated with a protamine zinc insulin reaction is mistaken for a slight cerebral vascular disturbance.

In treating a protamine zinc insulin reaction one must be mindful of a recurrence of hypoglycemia one to three hours following treatment of one episode. This is due to the continued prolonged effect of protamine zinc insulin. To coun-

*Table 66*  
INSULIN ACTION CURVES

Type of Insulin	Maximum Action (Hours)	Duration (Hours)
Crystalline zinc insulin	6	12
Modified insulin		
(a) 2:1 mixture NPH 50	10	18
(b) Globin insulin with zinc	10	20
Protamine zinc insulin	14	30

daily crystalline insulin requirement, one may then substitute two-thirds of this as a single daily injection of protamine zinc insulin, with a supplementary dose of crystalline insulin as indicated.

Table 67  
ILLUSTRATIVE CASES IN DIABETIC MANAGEMENT

Patient	Dietary Prescription			Carbohydrate Distribution				Insulin	Premeal Urine Sugar			Urinary Ketone Bodies		
	C	P	F	Brkf.	Lunch	Dinner	Bedtime		8 a.m.	12 n.	6 p.m.	8 a.m.	12 n.	6 p.m.
Severe, young diabetic male (weight 70 kg.)	220	90	80	1/3	1/3	1/3	..	CI 40 U. 8 a.m. 20 U. 12 n.	++	+	0	+	+	+
				3/4	3/4	3/4	3/4	PZI 40 U. 8 a.m.	+	++	0	0	0	0
				3/4	3/4	3/4	3/4	PZI 45 U. 8 a.m. CI 20 U. "	±	0	0	0	0	0
				3/4	3/4	3/4	3/4	NPH <sub>50</sub> 60 U. "	±	0	0	0	0	0
Mild, elderly diabetic female (weight 50 kg.)	220	80	60	2/4	2/4	2/4	2/4	PZI 20 U. 8 a.m.	±	+	0	+	0	0
	180	80	60	3/4	2/4	3/4	3/4	PZI 10 U. "	0	0	0	0	0	0
	160	90	70	3/4	3/4	3/4	3/4	PZI 0 U. "	±	±	0	0	0	0

teract this, frequent carbohydrate feedings should be given throughout the remainder of the day or night. Residual weakness, incoordination, and headache often follow a hypoglycemic attack.

Recurrent hypoglycemic attacks, with their attendant anxiety, headache, confusion, and loss of concentration power, represent a serious handicap to the working diabetic. The patient must be told about the prodromal symptoms so as to prevent a full-blown insulin reaction. Whenever exercise is anticipated, the patient should reduce the dose of insulin. Hypoglycemic attacks during the daytime call for a reduction of crystalline insulin, whereas those occurring in the afternoon, evening, and early morning hours are best prevented by reduction in the dose of modified insulin. If no weight gain has occurred, carbohydrate intake may be increased at the appropriate meal. A reduction in dietary fat will be necessary in patients who exceed ideal weight.

**Other Complications of Insulin Therapy.** Early in the treatment with insulin, a local reaction characterized by redness, swelling, pain, and nodule formation may occur at the site of insulin injections, particularly with protamine zinc insulin. These reactions persist for variable lengths of time and appear less and less frequently as the use of protamine zinc insulin continues (spontaneous desensitization). Where such local irritation is actually an allergic manifestation, itching is usually present also. *Hypersensitivity to insulin* may appear in the form of a generalized allergic reaction or, rarely, as an anaphylactic shock. Changing to an insulin derived from another animal species or to one prepared by a different manufacturer may be all that is necessary to remove

hypersensitivity reactions. Occasionally desensitization is required.

*Skin infections at the site of insulin injection* are distinct from the above reactions, and call for special treatment.

*Insulin lipodystrophy* is characterized by a complete atrophy of the subcutaneous fat at the site of insulin injection. Localized deep hollows are produced in the skin. This condition is more frequent in women and children. It is important to avoid these sites in subsequent insulin administration, and over a period of time these defects will gradually disappear.

*Insulin sensitivity* is related to the rapidity of response of the blood sugar to an injection of insulin. In severe juvenile diabetes, insulin reactions may occur quite frequently. In contrast, a mild diabetes of late adult life may be relatively insensitive to insulin.

*Insulin resistance* is observed in individuals in whom satisfactory diabetes control is attained only by the administration of extraordinarily large amounts of insulin. Severe infection and liver disease are the most common causes of this resistance. Pulmonary tuberculosis is another cause. Excessive anterior pituitary secretion (acromegaly), adrenal cortical hyperactivity (Cushing's syndrome), and thyroid overactivity may markedly increase the requirement for insulin. Antibodies to insulin have been described.

*Transient presbyopia* occurs in an appreciable number of patients during the initial period of insulin therapy. This disturbance is related to a reduced elasticity of the lens dependent upon an alteration in osmotic equilibrium between the lens and ocular fluids. The change is bilateral and

tends to disappear after two to four weeks of insulin therapy. It is wise to wait until the diabetes has been under satisfactory control for at least six weeks before obtaining prescription lenses if these are needed.

### TRAINING OF PATIENT

It is a relatively simple matter to obtain good regulation, provided a patient's coöperation has been obtained. By instructing a patient to test his urine for sugar and acetone in the morning on arising, again just before lunch, in the evening before dinner, and at night before retiring, fluctuations in blood sugar levels can be detected and adjustment of diet and insulin therapy may be made as indicated. It is not necessary for patients to carry on this multiple type of testing for any prolonged period unless regulation is extremely difficult. It is desirable for most severe diabetic patients to test the urine on arising. Simplified chemical outfits today allow the tests to be made with ease and rapidity.

The difficulty of obtaining satisfactory regulation in a diabetic under emotional stress is well known, and should be considered whenever unduly wide swings from hyperglycemia to hypoglycemia are encountered in a patient who is faithfully following his prescribed regimen. It is often impossible, under such circumstances, to obtain satisfactory regulation with any regimen until the psychologic and emotional difficulties have been dealt with.

### GENERAL HYGIENE MEASURES

The diabetic patient must ever keep in mind his propensity for infection. Keeping the number of infections at a minimum is largely dependent upon the individual's personal hygienic habits. Personal hygiene in the diabetic patient refers primarily to cleanliness. Careful and frequent cleansing of the skin should be emphasized. Immediate attention to all skin abrasions and the application of 75 per cent alcohol will often prevent serious sequelae. The nails should be kept clean but the cuticle should not be cut. All areas of pruritus should be kept clean, dry, and free from irritation. Good oral hygiene is helpful in reducing tooth infection and in delaying the onset of tooth decay. The lower extremities with their attendant vascular changes require a more special type of attention.

**Care of Feet.** In patients with diabetes mellitus, arterial changes progress more rapidly than in nondiabetics. Among the vessels frequently affected are those of the extremities. Care and attention to the feet may prevent long periods of disability. Every patient with diabetes should be given careful instruction in this matter. Simple rules include:

1. *Cleanliness:* Wash feet with warm, not hot or cold, water and a bland soap each evening. Dry thoroughly but gently between the toes. Then rub feet gently with rubbing alcohol. If the skin is dry, use lanolin or cocoa butter two or three times weekly.
2. Wear clean hose, loosely fitting and without seams or wrinkles.
3. Insert lambs wool between overlapping toes.
4. Avoid injuries to feet.
5. Cut toenails only with scissors or nail clippers, never with a knife, and only after a foot bath.

Pointed shoes and loose-fitting heels are dangerous and should be avoided. Corns are caused by ill-fitting shoes. Properly fitting shoes are most important, and protective pads are helpful. Corns should be treated only by an accredited chiropodist or surgeon. Epidermophytosis is best treated with cleanliness and appropriate medicated powder such as calcium propionate. Special exercises and measures for improving the circulation of the feet are an invaluable adjunct in many elderly patients.

### GENERAL CONSIDERATIONS

Most authorities attempt to eliminate glycosuria in so far as is practicable, and to restore the blood sugar to normal levels. There is, however, a feeling on the part of some that in children and in adults with vascular disease it is preferable to permit diet ad libitum with attendant glycosuria, provided sufficient insulin is given to ensure the utilization of at least 100 to 200 Gm. of carbohydrate. Although regulation of this type may be a necessary expedient under certain circumstances, it obviously does not restore internal metabolism to normal. Furthermore, it may increase the incidence of urinary tract infection.

Although there may be some disagreement as to the necessity for maintaining normal blood sugar levels in diabetic regulation, all authorities agree that the attainment of a normal serum cholesterol level is of utmost importance. It is

felt that long-continued elevation of the serum cholesterol level may play a significant role in the late-stage serious vascular complications. Therefore, in following the regulation of diabetic patients, frequent serum cholesterol determinations should be carried out. In the presence of persistent lipemia or hypercholesterolemia, dietary fat should be reduced, carbohydrate increased, and sufficient insulin administered to prevent hyperglycemia and glycosuria.

Physicians should have a clear understanding of the hardships involved in dietary restrictions, and the special nursing problems involved in making up to children and sensitive adults the loss of the pleasure of an unrestricted diet. They should also appreciate the effect on a patient of the knowledge that he has an incurable disease, and the feeling of indifference which is aroused, especially in children, by the regimen imposed by the disease. The patient and his family should be aware of the nature and frequency of negativism and personality changes in diabetic patients which accompany excessively low blood sugar levels. These are prone to occur immediately prior to meals and on arising in the morning if protamine zinc insulin is being used.

Patients with diabetes should understand clearly the risk involved for their progeny in marrying a diabetic or an individual with a family history of diabetes.

## COMPLICATIONS

### INFECTIONS

Poorly controlled or uncontrolled diabetic patients are susceptible to infections, particularly those involving the skin and urinary tract, and also tuberculosis.

**Pruritus.** This is a common symptom frequently observed among poorly regulated diabetics. Not uncommonly, skin infections develop from scratching such areas. *Pruritus vulvae* is frequently observed and may be very disturbing. Severe local skin irritation and infection are usually present. The pruritus usually vanishes within a few days following the disappearance of sugar from the urine.

**Epidermophytosis.** Although its occurrence is no more frequent among diabetics than among normal persons, epidermophytosis in a diabetic is much more serious since it provides a portal of entry for bacterial infections.

**Furuncles.** Repeated bouts of furuncles also suggest the diagnosis of diabetes, and are observed with great frequency among unregulated diabetics. Not infrequently, these may proceed to more extensive involvement, such as *carbuncle* formation.

**Urinary Tract Infections.** These are particularly prone to occur in poorly regulated diabetics. Bowen has observed an incidence of approximately 50 per cent among female diabetic patients. The treatment of pyelonephritis and cystitis in diabetics is identical with that of non-diabetics. It is essential, however, to keep the urine free from sugar for successful therapy.

Occasionally one may encounter a fulminating and often fatal form of renal infection, *renal necrotizing papillitis*, which is found in uncontrolled diabetics. It is characterized by the almost complete destruction of papillae with an ascending involvement of renal parenchyma.

**Cholecystitis and Cholelithiasis.** There is a high incidence of cholecystitis and cholelithiasis among diabetic patients. In addition to the obstructive symptoms which a stone may cause, a chronically diseased gallbladder might be a focus of infection, which may make regulation of diabetes more difficult. The possible relationship of chronic cholecystitis and cholelithiasis to pancreatitis must be given particular consideration in diabetic patients.

**Pulmonary Tuberculosis.** Diabetic patients, if poorly regulated, are susceptible to pulmonary tuberculosis, and a chest film should be taken once yearly as a routine prophylactic measure. In most instances, diabetes precedes the development of clinical tuberculosis, and tuberculosis is most likely to become manifest in the presence of weight loss and poor regulation of the underlying disease.

Whenever diabetic regulation becomes difficult or whenever there is an unexplained increase in insulin requirement, a hidden focus of infection should be suspected and searched for diligently.

## DIABETIC ACIDOSIS AND COMA

The treatment of a patient in diabetic coma must be highly individualized, and will vary greatly from patient to patient depending upon age, vascular status, the presence of infection, and the degree of acidosis. The general principles of treatment in diabetic coma are as follows:

1. Immediate and adequate insulin therapy
2. Treatment of acidosis, dehydration, and shock by means of parenteral fluid and electrolytes, and whole blood or plasma
3. Treatment of complicating infection with appropriate antibiotic therapy
4. Prevention of aspiration of vomitus by gastric aspiration
5. Institution of fluid therapy by mouth as soon as tolerated.

**Plan of Treatment: INSULIN THERAPY.** The first and foremost necessity is to administer adequate insulin immediately. A justifiable criticism of the treatment of diabetic coma in most institutions is the fact that insufficient insulin is used. Often a patient's life may be saved by the administration of 50 to 100 units of insulin by the attending physician prior to hospitalization or en route to the hospital. In 123 cases of coma treated at the Joslin Clinic, the average dose of insulin was 216 units in the first three hours.

As soon as the diagnosis of diabetic coma is established, 100 units of crystalline insulin should be given intravenously or subcutaneously if the blood sugar exceeds 500 mg. %. This should be accompanied by the subcutaneous injection of an additional 100 units of crystalline insulin if the carbon dioxide-combining power is less than 10 mM. per liter (22 vol. per 100 ml.). If the blood sugar level is between 300 and 500 mg. %, 50 to 100 units of insulin should be given intravenously and 50 units subcutaneously. With a blood sugar level below 300 mg. %, an initial dose of 50 units of crystalline insulin subcutaneously may be adequate, provided that severe acidosis is not present. Insulin should be given every hour thereafter in most instances. The hourly dosage should be gauged by following the change in blood or urine sugar levels. A practical rule of thumb in determining the subsequent insulin dosage is to administer subcutaneously 25 units of crystalline insulin in the presence of a 4 plus (red) reaction, 20 units for a 3 plus (orange), 15 units for a 2 plus (yellow), and 10 units for a 1 plus (green) urine sugar. In the presence of severe acidosis, or with the persistence of high blood sugar levels, it may be necessary to give as much as 100 to 200 units of crystalline insulin hourly. Once the blood sugar level approaches 200 mg. %, glucose and insulin or fruit juice, if tolerated, should be administered until the last trace of ketone bodies has dis-

peared from the urine. Insulin and glucose may be used in the proportion of 1 unit of insulin to 1 Gm. of carbohydrate in the presence of acidosis.

Modified insulin, such as protamine zinc or globin insulin, with a delayed type of action, is not recommended by the authors for initial use in diabetic coma since the action of these preparations is too slow to intervene effectively in early treatment, and the use of large amounts of protamine zinc insulin initially may predispose the patient to severe hypoglycemic reactions during the convalescent period. However, once hyperglycemia and ketosis have been corrected, modified insulin should be given as soon as possible, since the more sustained and somewhat smoother action of this type of insulin is of great advantage.

**FLUID THERAPY.** Dehydration and acidosis should be corrected by the use of intravenous fluids if the patient is comatose, and by oral fluids of the patient will retain them. Fluid therapy should be instituted immediately, in conjunction with insulin administration. The type of parenteral fluids used will depend upon the clinical signs and blood chemical changes. Most patients with severe ketosis and dehydration will respond to sodium chloride solutions alone. Sodium lactate or bicarbonate solutions in proper quantity added to isotonic saline will provide a ratio of sodium:chloride which corresponds closely to that of normal serum. This may be accomplished by adding 500 ml. of  $\frac{1}{6}$  M sodium lactate (1.9 per cent) or bicarbonate (1.3 per cent) to each liter of 0.85 per cent sodium chloride solution. Patients with very severe acidosis (i.e., a carbon dioxide-combining capacity of less than 5 to 10 mm. per liter) may be unresponsive to insulin until the acidosis is corrected. Under these circumstances, administration of sodium bicarbonate solution may prove lifesaving. It should be given intravenously in doses of at least 1000 to 2000 ml. of 1.3 per cent sodium bicarbonate solution.

It is advisable to add a potassium phosphate solution to the intravenous infusion whenever the diabetic coma has been treated for over a period of four or more hours, or when glucose solutions are used together with insulin in the treatment of acidosis and coma. It is well known that there occurs an immediate and marked withdrawal of potassium and phosphate from the serum with increased peripheral utilization of glucose (fig. 116), such as occurs with successful treatment of

diabetic coma. One may administer the following potassium phosphate solution safely and with benefit, provided adequate insulin has been administered to ensure a progressive fall in blood glucose level and provided the patient is voiding:

$K_2HPO_4$  2.0 Gm. per liter  
 $KH_2PO_4$  0.4 Gm. per liter  
Glucose 50.0 Gm. per liter

As soon as the patient is able to tolerate fluids by mouth, an effort should be made to administer foods containing relatively high potassium and phosphate content, such as orange juice, grape juice, bananas, and broth concentrates. The administration of whole blood should be considered if shock persists after the initial administration of adequate electrolyte and fluid substitution. It is desirable to follow changes in carbon dioxide-combining power at least every four to six hours. Supplementary sodium lactate or sodium bicarbonate solutions should be discontinued when the carbon dioxide-combining power attains a level of 25 mM. per liter or more. The hematocrit and hemoglobin should be followed every six hours as a guide to hydration. The administration of saline solution should be discontinued when the hematocrit approaches 45 per cent. A total of 4000 to 8000 ml. of fluid is usually required over the first 24 hours in severe acidosis and dehydration in order to establish normal hemoglobin or hematocrit concentration. In elderly patients, however, the rate of administration of fluids and the total quantity employed should be considered carefully. Too often, enthusiasm in correcting acidosis and dehydration too rapidly in these patients has induced heart failure or signs of pulmonary edema. It may be desirable to administer digitalis to elderly patients or patients with evidence of vascular disease.

The changes in blood sugar should be followed every two hours, if possible, and glucose should be added to the infusion whenever the blood sugar has fallen below 200 mg. % unless the patient is able to take carbohydrate by mouth. There is considerable debate as to both the advisability of glucose administration and the time at which supplementary glucose solutions should be used in diabetic ketosis and coma. Since there is a maximum rate at which glucose can be utilized by the body, it seems unnecessary to provide glucose in the first hour or two of treatment.

However, as soon as the blood sugar level begins to fall significantly or the glycosuria begins to decrease, supplementary glucose is indicated. The administration of supplementary glucose will decrease the ketosis more rapidly and restore glycogen depots. It is probable that in the past the failure to supply adequate potassium and phosphate, along with the B-complex vitamins, may have caused severe deficiency symptoms to appear when large quantities of glycogen were deposited in response to massive insulin therapy and intravenous glucose administration.

**Accessory Procedures in Treatment of Diabetic Acidosis and Coma.** Gastric lavage with diluted sodium bicarbonate, leaving a residue in the stomach, is useful in all patients. Patients in collapse should be treated with stimulants and the general measures employed in the treatment of shock should be followed. Infections should be treated vigorously by the administration of antibiotics. It is the authors' custom to administer immediately 300,000 units of long-acting penicillin in all cases of severe acidosis and coma after bacterial cultures have been obtained. Lumbar puncture should not be undertaken unless a cerebrovascular incident is seriously suspected, and then only a 22-gauge needle should be used. Fecal impactions of the rectum occur frequently and should be broken up.

**Aftercare.** The patient must be followed closely until he is completely responsive and the urine is free of acetone, with a glycosuria of 2 plus or less. At this point, the acute phase of the illness may be considered terminated. During the subsequent 12 hours, the patient should receive a soft diet which should include foods such as orange juice and salty broth. It is essential to begin with small feedings at frequent intervals. Intravenous fluid administration may be discontinued as soon as the patient is able to retain adequate quantities of food and liquid by mouth. Within 48 hours, it is possible to re-establish most patients on their standard diabetic regimen.

## DEGENERATIVE CHANGES

**Arteriosclerosis.** Degenerative vascular disease is a frequent complication of diabetes. This reflects in part the advanced age of diabetics as a group and in part the particular effect of diabetes in initiating or accelerating degenerative arterial changes. Atheromatous and patchy thickening of

the intima of the larger arteries predominates in diabetic patients. The first evidences of this process are usually seen in the vessels of the extremities and the ocular vessels. Recently the roentgenologic appearance of the pelvic vessels has been shown to serve as a good index of the vascular stage.

Heart disease leads as a cause of death among diabetic patients. Coronary artery disease is approximately five times as frequent in males as in females among the nondiabetic population, whereas the incidence of the disease in female diabetics is about as frequent as in men. It is thought that diabetic patients with extensive cardiovascular disease do better if the blood glucose level is not regulated too closely.

A renal syndrome characterized by hypertensive cardiovascular disease, anasarca, proteinuria, and diabetes of variable severity constitutes a dread complication afflicting both mild and severe diabetics of long-standing. Intercapillary glomerulosclerosis characterizes the Kimmelstiel-Wilson syndrome pathologically.

Advancing cerebral vascular disease is of particular importance in diabetes because of the ease with which vascular accidents may be confused with coma on the one hand and with hypoglycemia secondary to excessive insulin on the other.

**Gangrene.** Gangrene of the lower extremities is a serious and relatively frequent complication of diabetes. A small gangrenous area on the foot may totally incapacitate an otherwise relatively healthy diabetic patient. Intermittent claudication is a frequent precursor of arteriosclerotic gangrene. Prophylaxis in the care of the feet and legs, the avoidance of infections in the extremities, and the use of exercises designed to maintain and increase circulation to the legs and feet, in conjunction with good diabetic regulation, compose the principal methods of delaying the onset of this complication. It is essential to examine carefully the state of the circulation in the extremities of all diabetics, in which the use of the histamine flare test is often very helpful. Although vascular occlusion is the principal pathologic change accounting for diminished blood flow, it is not unusual to observe varying degrees of associated arterial spasm. If such is the case, great improvement of an otherwise hopelessly slow healing process may be obtained by lumbar sympathectomy.

**Ocular Complications.** Diabetic retinopathy and cataracts compose two of the more serious and not infrequent complications. Although poor diabetic regulation is no doubt an important contributory factor, it is distinctly disappointing to observe the development of this serious complication in relatively well-regulated patients. The retinopathy is particularly prone to occur in elderly diabetics with mild and often neglected diabetes of long standing. Retinal changes also appear to form an increasingly serious complication in younger diabetics.

Diabetic retinopathy is characterized by oval, punctate hemorrhages located deep in the retina, by shiny or waxy punctate exudates, by more extensive involvement of both veins and arteries with widespread exudate and hemorrhages (the so-called "retinitis proliferans"), and by "cotton wool" patches in diabetics with coexistent nephrosclerosis.

Cataracts occur in two forms: the senile cataract which is indistinguishable from that seen in elderly, nondiabetic patients; and the true diabetic cataract of relatively rare occurrence, which often forms rapidly and is seen predominantly in juvenile diabetics.

**Diabetic Neuropathy.** Neuropathic changes are common in diabetic patients, particularly among those over 40 and among the poorly nourished and poorly regulated. Vitamin deficiencies may contribute, but do not appear to be essential to the production of the neuropathy. Among the abnormal neurologic findings one may observe reduced or absent tendon reflexes, irregular and unequal pupils, cutaneous sensory changes, diminished vibratory sense, muscle tenderness, and foot drop (see table 68). Neurogenic bladder and pseudotabes occur in the long-standing cases. Postural hypotension and nocturnal diarrhea may also be encountered. It is not generally appreciated that the protein content of the spinal fluid is frequently increased, usually without accompanying changes in cell count or dynamics. Treatment consists essentially of careful diabetic regulation, a high protein intake, and supplementary vitamin therapy, especially large quantities of B complex. Liver extract may be worthy of trial. In early cases it is possible to reverse the changes. It may take weeks or months to effect maximum improvement. Paradoxically, it should be noted that symptoms may be aggravated following the institution of insulin therapy or im-

proved diabetic regulation. It has been postulated that this is due to an acute deficiency of essential substances precipitated by the rapid restoration to maximum carbohydrate utilization.

*Table 68*  
DIABETIC NEUROPATHIES

1. SENSORY CHANGES:  
Numbness, tingling, and paresthesias
2. NEUROMUSCULAR DYSFUNCTION:  
Muscular cramps, tenderness, aching, weakness, paralysis; occasional "shooting pains"; diminished or absent tendon reflexes
3. AUTONOMIC NERVE DISEASE:  
Edema; decreased or absent sweating; intolerance to temperature extremes; night sweats; skin changes due to decreased function of sebaceous glands and vascular lability; miotic, occasionally irregular, pupils, reacting sluggishly to light
4. ORTHOSTATIC HYPOTENSION OF TACHYCARDIA:  
Faintness, dizziness, syncope on standing
5. GENITOURINARY AND SPHINCTER DISTURBANCES:  
Sexual impotency; urinary and fecal incontinence; atony and paralysis of bladder
6. GASTROINTESTINAL DYSFUNCTION:  
Severe constipation; chronic diarrhea (nocturnal); anorexia and nausea
7. BONES AND JOINTS:  
Degenerative joint disease (neuropathic foot)

#### SURGERY AND DIABETES MELLITUS

Diabetic patients may be affected by any disease, but there are certain surgical conditions, such as gangrene, cholecystitis, and cholelithiasis, to which they are more prone than the average person. The present average mortality rate in surgical diabetics is practically the same as the over-all average for the general population. Certainly diabetes is not a contraindication, therefore, to any necessary operation, and if the case is an emergency there is no need for delay.

The surgical risk is increased in diabetics in the presence of poor regulation, obesity, arteriosclerosis, or cardiovascular disease. Preoperative care should include adequate dietary and insulin regulation. The selection of anesthesia should be carefully considered so as to eliminate, in so far as is possible, anoxia, acidosis, or liver damage. Cyclopropane, nitrous oxide, ethylene, spinal anesthesia, and local anesthesia are the methods of choice.

Insulin administration may be regulated in one of several ways. Approximately one half of the total daily dose of crystalline or protamine zinc insulin may be given on the morning of operation, and the other half following operation. After this,

no further insulin need be given, unless required by urine and blood sugar tests, until the following day, when the usual morning dose is resumed. The blood or urine sugar should be determined following operation and at approximately four-hour intervals. Crystalline insulin should be given as indicated; that is, approximately 15 units if the urinary reaction is red, 10 units if it is yellow, and 5 units if it is yellow-green to Benedict's solution. If the diabetes is relatively mild and well controlled, and the operation is scheduled for early morning, food and insulin may be omitted until the operation is completed, at which time the usual amount of insulin and food is given. Some authors advocate omitting protamine zinc insulin on the day of surgery and for several days following, and prefer to control the diabetes with crystalline insulin at approximately four-hour intervals, depending upon changes in the urine sugar. No attempt should be made to keep the urine rigidly sugar free for a day or two following operation.

The diet should be adequate in every respect, and, if possible, should be continued at least up to 12 hours preoperatively. If it is desirable to omit food the morning of operation, 1 liter of 5 per cent glucose in water or saline should be given intravenously. Following operation, food and fluid should be given either orally or intravenously, according to the dictates of the operative procedure and the condition of the patient. At least 150 Gm. of carbohydrate should be given daily, either orally or parenterally. The maintenance of proper fluid intake is essential in the care of diabetic patients following surgery. The need for extra vitamins and minerals, particularly thiamine and potassium, should not be overlooked either preoperatively or postoperatively.

Amputation of a part of or a whole extremity is often necessary in diabetic patients, and is usually indicated if gangrene or osteomyelitis is present. If the infection or gangrene is located in the toe, transmetatarsal amputation has proved successful if adequate circulation is present. If the condition extends higher than the toes, a low thigh amputation provides the best chance for subsequent well-being.

The diagnosis of acute abdominal lesions occasionally presents some difficulty in the diabetic patient. Many of the signs and symptoms of diabetic acidosis are similar to those resulting from abdominal emergencies. Abdominal pain and ten-

derness, nausea and vomiting, tachycardia, and leukocytosis may all be found in diabetic acidosis. Fever may, of course, be due to infection elsewhere in the body. On the other hand, an abdominal emergency will be suggested by a sharp localization of the pain and by the lack of improvement after several hours of adequate diabetic control.

### DIABETES MELLITUS AND PREGNANCY

The problem of management during pregnancy has assumed increasing importance during the past two decades, as diabetic patients have become capable of procreation. Prior to insulin therapy infertility in both male and female diabetics was common. With insulin therapy there has been a marked reduction in mortality and morbidity, especially among young diabetics. The increasing number of diabetics maintained in excellent health has, of course, increased the importance of considering the effect of the disease upon the mother and fetus.

The first problem which must be answered is one of genetic, social, and ethical significance. Diabetics should not be encouraged to procreate diabetics. Hence the family history of the non-diabetic partner is of great importance. A diabetic with a spouse possessing a positive family history of diabetes should not bear children. A negative family history for diabetes in the non-diabetic parent permits the serious consideration of procreation without danger of diabetes occurring in the offspring.

Today pregnancy carries but slightly added risk for the well-managed diabetic mother. In the pre-insulin era, maternal mortality among diabetics often reached 25 to 30 per cent, whereas today less than 1 per cent of diabetic mothers succumb during pregnancy. In contrast, however, fetal mortality is still very high. Stillbirths among diabetics are six times as common as among nondiabetics, and toxemia of pregnancy appears to occur in 12 to 50 per cent of cases. White and Smith and Smith have reported abnormal serum prolactin (chorionic gonadotrophin) and sex hormone imbalance to be associated with the increased fetal mortality rate among diabetics. In White's series 96 per cent of diabetic patients with normal sex hormone balance had surviving fetuses, whereas 50 per cent fetal mortality rate was observed in patients with marked hormonal

imbalance. Correcting the sex hormonal imbalance with estrogens and progesterone resulted in a reduction to 10 per cent fetal mortality.

**Diagnosis.** In patients who are not known to be diabetic, the diagnosis of diabetes mellitus may offer some difficulty because of the frequency with which glycosuria is observed among non-diabetic pregnant women. The diagnosis may be established with certainty only by repeated analyses of the fasting blood sugar level or a glucose tolerance test (see Melituria, p. 712). By these means it is possible to distinguish between the glycosuria associated with lowered renal threshold during pregnancy and the true diabetes mellitus. In the former the fasting blood sugar levels and the glucose tolerance curve will be normal.

**Treatment.** The treatment of pregnant diabetics entails the same general health measures as those recommended for nondiabetic pregnant patients. It is desirable to maintain a high intake of protein (i.e., at least 2 Gm. per kg. of body weight per day) and an adequate intake of calcium, iron, and iodine. The diabetes is regulated throughout pregnancy with insulin; because of the lowered renal threshold for glucose it is wise not to attempt to keep the urine free, but rather to give adequate carbohydrate and insulin to ensure the utilization of at least 200 Gm. of carbohydrate daily. Such a regimen will prevent acidosis despite mild glycosuria. It is often difficult to manipulate the diet satisfactorily so as to avoid hypoglycemia on the one hand and excessive weight gain on the other. Excessive gain in weight appears to predispose to complications of pregnancy such as toxemia and large babies.

Care of a diabetic through the first trimester is perhaps the most difficult because of nausea and vomiting. It is essential to maintain an adequate caloric intake during this period, and, if frequent small feedings are not well tolerated, intravenous glucose must be administered at regular intervals. Because of the unpredictability of the nausea and vomiting, it is preferable to use small doses of crystalline insulin several times daily, rather than to attempt to use a single injection of protamine zinc insulin with possible hypoglycemic reaction if food is not retained.

The second trimester offers less difficulty, and little change in carbohydrate or insulin requirement is noted. In the third trimester the insulin requirement usually increases, and good control of the mother's diabetes prevents an undue load

on the fetal pancreas. Spontaneous hypoglycemia in the newborn may be avoided by careful regulation of the mother's diabetes during the last trimester.

It is of utmost importance to detect preeclamptic toxemia, since treatment of this complication offers great opportunity to reduce infant mortality. White believes this state may be indicated by the appearance of excessive prolan in the urine with reduced estrogen and pregnanediol. These changes appear to precede the increase in blood pressure, proteinuria, and edema so characteristic of preeclamptic toxemia. Because of the great practical difficulty in obtaining satisfactory hormonal analyses, the question of whether one is justified in routinely following the supplementary hormonal therapy as a prophylactic measure in all pregnant diabetics is quite naturally raised. In the authors' opinion, little harm would ensue from such a program, and the probability of obtaining a viable fetus would certainly be greatly increased. The following therapeutic program is outlined by White for those patients who show abnormal hormone balance: Up to the twentieth week of pregnancy, 5 mg. of diethylstilbestrol and 5 mg. of progesterone should be given intramuscularly daily; from the twentieth to the twenty-third week, 10 mg. of each; from the twenty-third to the twenty-sixth week, 15 mg. of each; from the twenty-sixth to the thirty-first week, 25 mg. of each; and thereafter, 50 mg. of each up to the time of delivery. Because of the high cost of prolonged progesterone therapy, the use of diethylstilbestrol alone has been recommended. Preliminary observations indicate its effectiveness. Oral preparations require greater dosage. During the thirty-eighth week Cesarean section is performed if delivery has not started spontaneously.

Normal labor and Cesarean section should be treated as any emergency or operation, the basic principles being the administration of carbohydrate by mouth or of glucose intravenously, the administration of crystalline insulin, the maintenance of hydration with hypotonic sodium chloride solution, and the administration of blood plasma as indicated.

#### DIABETES IN CHILDHOOD

Diabetes in childhood differs from that seen in the adult in being in general more severe and subject to more rapid and wider fluctuations. Dia-

betic children make up approximately 5 per cent of the diabetic population in this country. The peak age is approximately 12 for girls and 14 for boys, thus corresponding to the most rapid periods of growth. These observations correlate well with the theory that overactivity of the anterior pituitary and its satellite glands plays an important role in unmasking the predisposition to the disease.

Of particular importance is the fact that the patient is first seen in most instances in acidosis or coma; that protein depletion may be very great, necessitating the administration of at least 3 Gm. per kg. of body weight for prolonged periods to make up for an accumulated deficit and to provide for adequate growth. Furthermore, the criteria of good management in the adult (i.e., normal blood sugar level and absence of glycosuria) are much less important in judging the effectiveness of treatment in children with diabetes than is the restoration of normal growth rate and freedom from acidosis.

Diabetic children, at the time the disease is diagnosed, are inclined to be above average in height but below average in weight. Hepatomegaly and splenomegaly are common. Hepatomegaly disappears rapidly on a good therapeutic regimen, and is thought to be due to fatty infiltration.

Of great importance in the management of diabetic children is the physician's attitude toward developing a healthy personality in the child. The presence of a chronic incurable disease, the necessity for daily injections of insulin, the occasional periods of hospitalization, and the constant necessity for diet regulation can be balanced effectively only by continued understanding and help on the part of both physician and parents. It is in this realm that the idea of greater latitude in diet is perhaps of much greater help in personality development than the small chemical advantage to be obtained by undue concern over matters of less importance. Combined with such a liberal attitude in respect to carbohydrate ingestion should be a serious appreciation of the need for continued good regulation if the complications which plague juvenile diabetics are to be prevented or postponed. Satisfactory criteria of management include:

1. Maintenance of ideal weight and growth rate.

2. Healthy psychologic development.
3. Prevention of acidosis, coma, and insulin reactions.
4. Maintenance of normal serum cholesterol level.

Diet calculations should be made on the basis of ideal weight, not actual weight, and should include supplementary minerals and vitamins. Intermediate nourishment should be arranged. Protamine zinc insulin has been of great aid in reducing the number of injections and in preventing overnight hypoglycemia. It is possible that in children the modified protamine insulins and globin insulin may be very useful, since relatively larger doses may be given without inducing overnight hypoglycemia.

### HEMOCHROMATOSIS

It is important to detect hemochromatosis when it is a cause of diabetes mellitus, as the course of the disease and the outlook vary considerably from that of uncomplicated diabetes. The signs which should alert one are increasing

pigmentation, hypogonadism, hepatomegaly, and relative refractoriness to insulin. The disease occurs predominantly in males over 30 years of age (see Chapter 84).

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## 60

### Hyperinsulinism

George W. Thorn and Peter H. Forsham

Pathology  
Clinical Picture  
Diagnosis  
Treatment

The maintenance of a constant blood sugar level is one of the essential conditions for the preservation of homeostasis. Reduction in blood sugar levels to low or lower than normal values, regardless of the mechanism, initiates a marked autonomic reaction accompanied by a wide variety of symptoms. The symptomatology associated with any given reduction in blood sugar varies with the rate of fall and with the individual susceptibility of the patient.

The blood sugar level is at any one time the resultant of three physiologic processes: (1) the

utilization of glucose by muscle, liver, brain, and other organs; (2) the mobilization of glucose from liver glycogen by glycogenolysis; and (3) the increased secretion of insulin by the islets of Langerhans, enhancing glucose utilization, or the decreased secretion of its physiologic antagonist such as the pituitary glycostatic factor or adrenal cortical steroids tending to maintain blood sugar.

*Functional hypoglycemia* is a common physiologic disorder in which there is excessive insulin secretion in response to an elevation of the blood sugar following meals or periods of excitement. Over 90 per cent of cases with hypoglycemic manifestations fall into this group. A poor liver glycogen reserve occasionally causes hypoglyc-

mia, even though the amount of insulin secreted is normal.

*Hyperinsulinism* is a rare clinical entity arising from the continued excessive secretion of insulin, caused by a tumor or diffuse hyperplasia of the islets of Langerhans. In 1924 Harris, having observed the syndrome of insulin-induced hypoglycemia in a diabetic patient, postulated the existence of spontaneous hypoglycemia due to endogenous overproduction of insulin. Wilder, in 1927, reported a case of spontaneous hypoglycemia caused by cancer of the islets of Langerhans. Two years later Graham successfully removed a benign adenoma of the islet cells and cured a patient of recurrent bouts of hypoglycemia.

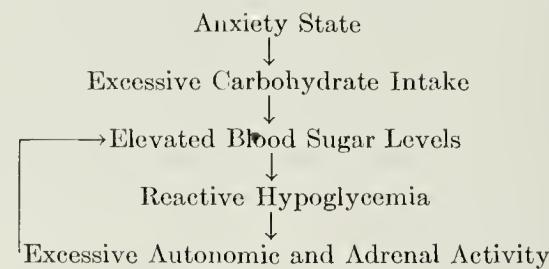
**Pathology:** FUNCTIONAL HYPOGLYCEMIA. In cases of functional hypoglycemia, as a rule, no pathologic changes are demonstrable in the islets of Langerhans. Parasympathetic overactivity determines excessive insulin secretion. Rare cases of cirrhosis, often of the biliary type, show poor glycogen storage leading to hyperglycemia immediately after meals, and subsequent hypoglycemia. Fixation of liver glycogen, as in von Gierke's disease, is a rare cause of reactive hypoglycemia.

**HYPERINSULINISM.** Hyperinsulinism is due almost always to islet-cell tumor. These tumors are usually encapsulated and very vascular, with a resultant purplish color. They are mostly 0.5 to 2 cm. in diameter and firmer than the normal pancreas. Most of the tumors are located in the body and tail of the pancreas. The tumors are usually benign adenomas, but they may be malignant and occasionally metastasize. In malignant tumors the metastases are found in the local lymph nodes and in the liver. In a large series of 149 cases of proved islet-cell tumor, 106 were benign adenomas (91 single and 15 multiple). In 28 cases the tumors were microscopically malignant, but grossly and clinically appeared benign. In 15 of the cases (10 per cent) the tumors were definitely malignant. Only 11 cases were due to diffuse hyperplasia. The age range was between 10 and 57 years, with the majority of cases occurring in the middle-age group.

**Clinical Picture:** FUNCTIONAL HYPOGLYCEMIA. This condition is characterized by weakness and faintness accompanied by symptoms of adrenergic overactivity, such as tachycardia, trembling, anxiety, palpitations, and premature beats, occurring approximately two hours after a meal

or following periods of emotional or psychologic upheavals. Ingestion of carbohydrate will relieve the symptoms within five minutes, but unless more food is taken subsequently the attacks will recur, thus establishing a vicious cycle (table 69). The patient frequently is of the asthenic, introspective type.

Table 69  
CYCLE OF FUNCTIONAL HYPOGLYCEMIA



**HYPERINSULINISM.** Hyperinsulinism due to islet-cell adenoma is characterized by an insidious onset, with periodic attacks which gradually become more frequent and more severe. Symptoms include weakness and excessive fatigue, nervousness, anxiety, tremulousness, faintness, nausea, sweating, syncope, circumoral numbness, epigastric pain, and palpitation. More severe manifestations of central nervous system disturbance include irritability, confusion, diplopia, nystagmus, aphasia, mania, convulsions, unconsciousness, and coma. Once the "attack pattern" has developed, it usually remains the same in any given patient. The attacks occur predominantly in the fasting state, and symptoms are attributable to hypoglycemia and resultant autonomic stimulation. Between attacks there may be no signs or symptoms. Patients often show profound personality changes and usually become obese from the frequent ingestion of food in an effort to prevent an attack.

**Diagnosis:** FUNCTIONAL HYPOGLYCEMIA. The diagnosis of functional hypoglycemia is indicated by the clinical picture of weakness and faintness two to three hours following the ingestion of carbohydrate. This is associated with some lowering of the blood sugar level. In contrast, the fasting morning blood sugar level is normal. An intravenous glucose tolerance test shows a rapid rise and a precipitous fall in blood sugar (past-pointing type). Patients exhibit normal sensitivity to injected insulin. Intravenous injection of 0.1 unit per kg. of body weight will lead to a 50 per

cent fall in fasting blood sugar within one-half hour. Epinephrine (0.3 mg. intramuscularly) will lead to a rise in fasting blood sugar of 50 to 100 mg. within one-half hour, indicating normal liver glycogen storage. In severe hepatic disease, glycogen storage may be impaired, and consequently one may observe reactive hypoglycemia, fasting hyperglycemia, and increased insulin sensitivity.

The majority of patients suspected of organic hyperinsulinism usually are discovered to have functional hypoglycemia associated with evidence of emotional and psychologic disturbances.

**HYPERINSULINISM.** Attacks of hyperinsulinism occur characteristically in the postprandial state associated with a fasting blood sugar below 50 mg. %, and there is immediate recovery from an acute attack upon the administration of glucose. This represents the triad of Whipple without which the diagnosis cannot be entertained. Hypoglycemia will occur regularly following a prolonged fast in hyperinsulinism, but such fasting will not induce functional hypoglycemia. Such patients often show a decreased sensitivity to insulin in the insulin tolerance test mentioned above. Glucose tolerance tests are not diagnostic. The final diagnosis is made at surgical exploration with identification of the small, firm adenoma by palpation of the pancreas. Tumors of the islet of Langerhans have been misdiagnosed as hysteria, neuroses, psychotic state, alcohol intoxication, brain tumor, epilepsy, encephalitis, duodenal ulcer, and hypoparathyroidism. The presence of severe hypoglycemia after an overnight fast is not observed in any of these conditions, but does occur in Addison's disease, pituitary insufficiency, and high-grade hepatic failure.

**Treatment: FUNCTIONAL HYPOGLYCEMIA.** The weight should be restored to normal in the frequent cases in which obesity is present. In general, the patients do well on a high-protein,

high-fat, low-carbohydrate diet and by the strict avoidance of high carbohydrate intake at any one time which would tend to raise the blood sugar unduly and thus lead to a more marked reactive hypoglycemia through excessive insulin secretion. The administration of parasympathetic or mimetic agents, such as tincture of belladonna every six to eight hours, using two less than the number of drops found to induce poor vision in the particular patient, is of benefit in decreasing excessive insulin secretion. Real help will be derived from assistance directed at correcting the emotional and psychologic difficulties.

**HYPERTHYROIDISM.** Once established, hyperinsulinism must be treated by surgery without delay because of the possibility of malignant change or metastases, further irreversible damage to the central nervous system due to severe hypoglycemic episodes, the deleterious effect of reactive sympathetic discharge on the heart of older patients with coronary insufficiency, and the increased obesity which will make surgical management more difficult. After adrenalectomy or subtotal pancreatectomy, the patient is usually cured except for rare cases of multiple tumors which are usually located in the head of the pancreas. In approximately 20 per cent of the malignant cases, follow-up observations have failed to reveal a recurrence of symptoms or tumor.

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# 61

## Diseases of the Testes

George W. Thorn and Peter H. Forsham

History
Physiology
Hypogonadism
Etiology
Clinical Picture
Diagnosis
Differential Diagnosis
Treatment
Hypergonadism
History
Etiology
Clinical Picture
Diagnosis
Differential Diagnosis
Treatment
Neoplasms of the Testes
Diagnosis
Treatment

The testis proper is functionally and anatomically composed of two units—namely, the seminiferous tubules having spermatogenic function, and the interstitial or Leydig cells possessing a hormonal function. It is well established that the anterior pituitary exerts a regulatory control over these structures. Interference with the function of the seminiferous tubules results only in disturbed spermatogenesis. In contrast, dysfunction of the interstitial or Leydig cells may induce far-reaching bodily changes. Hence a study of the endocrine disorders of the testes is limited to hypogonadism and hypergonadism associated with increased or decreased secretion of testicular androgenic steroids (testoids). Whether or not the Sertoli cells of the seminiferous tubules in man liberate a hormone is not known.

**History.** Although castration has been known to produce the eunuch since Biblical times, it was not until the work of Berthold in 1849 that this effect was explained as a humoral deficiency. The historical importance of the testes is illustrated by the fact that the birthday of endocrinology traditionally is considered to be June 1, 1889, when Brown-Séquard reported before the Société de Biologie de Paris the astonishing degree of rejuvenation which he observed in himself following subcutaneous injections of a Pasteur filtered dog testis suspension. The potency of this preparation may be questioned, but the observation is important as a landmark in the science of endo-

crinology. The first unquestionably potent androgenic preparation was prepared from bulls' testes by McGee in 1927. Later, David, Butenandt, and Ruzicka obtained similar material from human urine, crystallized it, and ultimately synthesized it from cholesterol.

**Physiology.** It appears that normal anterior pituitary function is necessary for the maintenance of normally functioning seminiferous tubules and Leydig cells. Evidence suggests that the seminiferous tubule activity is dependent upon follicle-stimulating hormone (FSH) and that the secretion of androgens by the Leydig cells is dependent upon anterior pituitary luteinizing hormone (LH), also known as interstitial cell-stimulating hormone (ICSH) (fig. 117). Nor-

### ANTERIOR PITUITARY

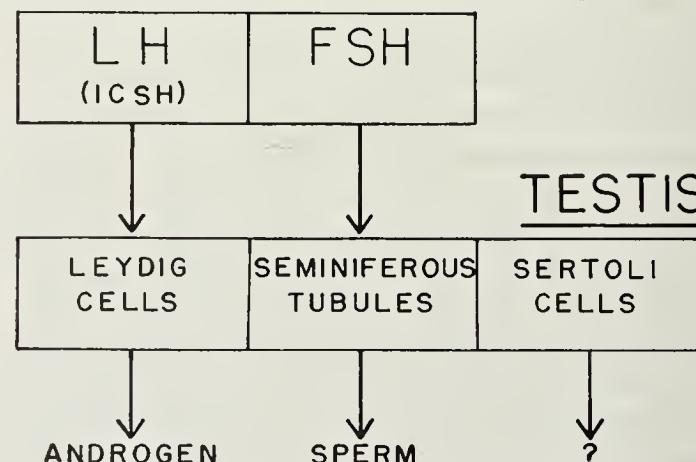


FIG. 117. Scheme showing anterior pituitary-testis relationship.

mal androgenic secretion or interstitial cell function is indicated by the presence of normal libido, secondary sex development, and a normal 17-ketosteroid excretion in the urine. In this respect, however, it is to be noted that approximately two thirds of the 17-ketosteroid excretion appears to be derived from androgenic (reticular) cells of the adrenal cortex, and only one third from the Leydig cells of the testes. Thus the interpretation of a diminished 17-ketosteroid ex-

cretion must take into account the state of adrenal cortical function.

Normal seminiferous tubular function is suggested by normal testicular size, as the size is for the most part dependent on tubular integrity; and is further suggested by a normal urinary FSH level, normal excretion of spermatozoa (dependent also on normal androgen production) and a normal testicular biopsy.

### HYPOGONADISM

**Etiology.** Gonadal deficiency may be the result of absence or destruction of testicular tissue, or atrophy consequent to pituitary insufficiency; and it may be due to either a disturbed tubular or a disturbed Leydig cell function, but usually involves both. Primary hypogonadism is associated with normal or increased anterior pituitary activity. This is measured routinely as urinary FSH, since the determination of LH is impracticable for clinical purposes. Hypogonadism secondary to pituitary failure is associated with atrophic gonads and low or absent FSH excretion.

Primary deficiency of testicular tissue or function may result from a genetic or embryologic defect or from hormone excess affecting the fetus in utero; or later in life may result from inflammation and destruction following infections such as mumps, syphilis, and tuberculosis; traumatic injury; x-ray or other irradiation; neoplasm; or as a consequence of surgical castration. Hypogonadism secondary to pituitary insufficiency is associated with destructive lesions in or about the anterior pituitary gland, or with pituitary failure secondary to x-ray irradiation or chronic disease with starvation, inanition, and vitamin deficiency. Diabetes mellitus or dysfunction of either the thyroid or adrenals may lead to hypogonadism.

**Clinical Picture.** Male hypogonadism may be classified conveniently according to the age of onset, since in general the severity of the manifestations is inversely proportional to the age at onset of the deficiency. Eunuchism usually refers to complete loss, whereas eunuchoidism refers to partial loss, of testicular function (fig. 118).

**PREPUBERTAL HYPOGONADISM.** When hypogonadism is prepupal, testicular deficiency occurs before normal development of the sex organs has been completed; and when it occurs secondarily to pituitary insufficiency from a suprasellar tumor, it is known as Froehlich's syndrome. The

testes are absent or extremely small, and the penis and other accessory sex organs are hypoplastic. The skin is delicate. There is deficiency or absence of pubic, axillary, and facial hair, and the voice retains its juvenile quality. Characteristically there is exaggerated length of the extremities, with broad hips, occasionally girdle obesity, and often gynecomastia; and the general body configuration tends more toward that of the female type, although occasionally the patients may be tall and thin. Sexual activity usually remains dormant.

**POSTPUBERTAL HYPOGONADISM.** With the onset of androgenic deficiency postpubertally, the changes are less striking. Atrophy or hypoplasia of the genitalia and accessory sex organs occurs. The small-sized prostate is noteworthy on examination. There is retarded beard growth, diminished potency, thinning of the skin with decreased pigmentation, and diminished or absent axillary and pubic hair. There is a failure to grow hairs on the antitragus of the ear (Hamilton's sign). In males with normal androgenic function, long hairs develop in this region after the age of 25 or 30.

**MALE CLIMACTERIC.** Vasomotor and psychologic disturbances are seen much less commonly in the male than in the female climacteric. This no doubt is due to the more gradual decline in sexual function of men as compared with the more abrupt termination of the cycle in females. Characteristic changes in the male climacteric are functional rather than structural. This condition is not common, and varies greatly among individuals.

**STERILITY WITHOUT EUNUCHOIDISM.** In this condition there is chiefly a seminiferous tubular deficiency without hypoleydigism. This is observed frequently in cryptorchism in which one or both testes fail to descend into the scrotum. Primary cryptorchism is not incompatible with the normal development of all accessory sex characteristics; whereas cryptorchism secondary to hypophyseal deficiency is likely to be associated with hypoleydigism and therefore to be evidence of eunuchoidism. Recently Klinefelter has described a syndrome characterized by atrophic sclerosis of the seminiferous tubules with normal Leydig cells and normal masculinization, but accompanied by gynecomastia and associated with high anterior pituitary follicle-stimulating hormone, normal or somewhat diminished 17-keto-

steroid excretion, and aspermatogenesis. The etiology of this syndrome is still obscure, but it appears to be hereditary.

**Diagnosis.** Hypogonadism may be diagnosed easily by the clinical features of diminished to absent secondary sexual characteristics, small, atrophic testes, and often classic facies. The face is smooth; the beard is absent or slight; there is an abundance of hair on the head, with a low temporal hairline; there is a juvenile appearance to the face, but with premature lines. The skin is thin and does not tan on exposure to the sun, and the nails are brittle. The musculature may be poor and atonic. The diagnosis of primary hypogonadism as opposed to that secondary to pituitary causes is dependent chiefly upon the demonstration of an absence of multiglandular defects, a normal FSH excretion, and failure to respond to pituitary or chorionic gonadotrophins. Hypofunction of the seminiferous tubules may be suspected from oligospermia or aspermia, and proved by testicular biopsy.

**Differential Diagnosis: CIRRHOSIS AND HEPATIC DISEASE.** It is now well established that disease of the liver may induce androgenic deficiency. It appears that this is due in part to a difference in the metabolism of estrogens and androgens whereby the former persist, leading to a marked increase in estrogenic-androgenic ratio. It is also possible that nutritional factors, especially the lack of absorption of vitamin E, play a role.

**DELAYED PUBERTY.** Many boys do not enter the pubertal period until 16 or 17 years of age. Their sexual development thereafter is normal, however. Overanxious parents and physicians often institute treatment unnecessarily in such cases. This is particularly true of very obese boys.

**IMPOTENCY.** Many patients with psychologic difficulties complain of diminished or absent libido and impotency. It is a well-known clinical observation that patients who complain of impotency or diminished libido rarely have hypogonadism. Patients with true hypogonadism are less likely to be aware of or to complain of their impotency.

**Treatment.** Treatment of specific infections and neoplasms and the correction of any generalized metabolic, nutritional, or endocrinologic disturbance should precede further therapy. In primary testicular hypogonadism the etiology of which cannot be corrected, substitution therapy with testosterone should be used. In hypogonad-

ism secondary to pituitary failure, however, an attempt to restore normal testicular function by appropriate pituitary-stimulating hormones should be made first.

Hypogonadism requiring substitution therapy (eunuchism, eunuchoidism, impotence from glandular causes, the male climacteric, cryptorchism, and hypopituitarism which fail to respond to gonadotrophins) may be adequately treated with 10 to 25 mg. of testosterone propionate given intramuscularly three times a week, or with its equivalent, as one of the other available testosterone preparations (see table 70) (figs. 118, 119). Testosterone

Table 70  
TESTOSTERONE PREPARATIONS COMMERCIALLY  
AVAILABLE (SYNTHETIC)

1. Testosterone propionate, in oil, in 1 ml. ampuls and 10 ml. vials containing 5, 10, 25, or 50 mg. per ml.  
Dose: 10 to 25 mg. intramuscularly three to five times per week.
2. Testosterone or testosterone propionate pellets, 75 mg. each, for subcutaneous implantation. Six pellets are equivalent to 25 mg. of testosterone propionate injected intramuscularly three times per week, and last three to nine months.
3. Testosterone or testosterone propionate tablets for sublingual absorption, 3, 4, 6, and 10 mg. tablets.  
Dose: 3 to 10 mg. one to four times daily.
4. Methyltestosterone tablets for oral administration, 10 and 25 mg. tablets.  
Dose: 10 to 100 mg. daily.
5. Testosterone microcrystals, in aqueous saline suspension, in 5, 10, and 15 ml. vials.  
Dose: 25 mg. two to three times per week.

should be used in the treatment of the male climacteric only after careful evaluation of the prostate has been made. Although testosterone has never been shown conclusively to produce carcinoma, cancer of the prostate is known to improve following orchidectomy. In certain cases of hypogonadism, small doses of testosterone may restore or preserve spermatogenesis, whereas the larger dose ordinarily employed in substitution therapy may depress or injure spermatogenesis.

Testosterone therapy, because of its striking nitrogen-retaining effect, is often employed in debilitating diseases without hypogonadism to facilitate restoration of protein reserves.

The administration of testosterone results in increased urinary 17-ketosteroid excretion; this is true of all forms of commercially available testosterone except methyltestosterone.

The dosage of testosterone should be increased

until the desired effect is obtained, or until undesirable side effects are produced. These include: (1) acne vulgaris, (2) masculinization in women, (3) edema (excess salt and water retention), (4) injury to normal testis leading to azoospermia,

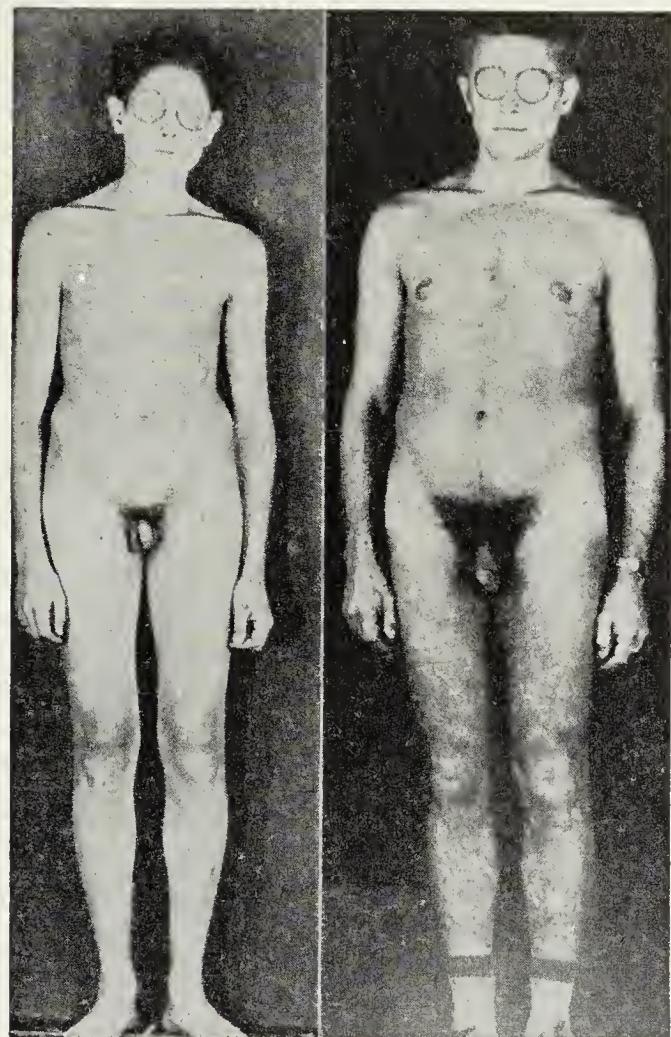


FIG. 118 (Left). Male, age 25 years, with eunuchoidism, untreated. (Courtesy, Werner: *Am. J. Med.*, 3:52, 1947.)

FIG. 119 (Right). The same patient, age 30 years, after male hormone therapy for five years. (Courtesy, Werner: *Am. J. Med.*, 3:52, 1947.)

(5) possible hypermetabolism, and (6) possible liver injury from methyltestosterone.

In the treatment of cryptorchism it is desirable to give 1000 to 1500 I.U. of chorionic gonadotrophin alone or in combination with pituitary gonadotrophin (see Chapter 63, p. 648) daily for two to three weeks to determine whether descent of the testes will occur. Even if it does not, such treatment so improves the vascular supply to the cryptorchid testes that plastic surgery is greatly facilitated. Patients with hypogonadism suspected of being secondary to pituitary failure should be tested with chorionic gonadotrophin in a dosage of 1000 I.U. daily for three weeks and

then three times weekly for two to three months. This form of therapy should be stopped at that time if it has not improved gonadal function.

### HYPERGONADISM

**History.** Two types of hormonal overproduction are observed with tumors of the testes—namely, increased androgen production with tumors of the Leydig cells, and increased gonadotrophic substances with certain teratomas. The earliest report of a case of Leydig cell tumor was described by Chevassu in 1906. In 1943 Pierre Masson showed that concomitant with the clinical signs of increased androgen production there was a greatly increased urinary excretion of androgenic-like material.

The first chorioepithelioma of the testis was described in 1902 by Schlagenhauf, and the close endocrinologic relationship between this tumor and placental chorioepithelioma of women was pointed out in 1930 by Zondek and by Heidreich. These tumors are associated with a high titer of gonadotrophin in the urine.

**Etiology.** Hypergonadism or, more truly, hyperleydigism is associated in almost all instances with a tumor of testicular tissue. Occasionally it may be observed in association with tumor or inflammatory lesions in the hypothalamic regions. In these circumstances it is assumed that mechanical stimulation of the adjacent anterior pituitary initiates increased production of pituitary gonadotrophins with consequent excessive development and activity of both Leydig cells and seminiferous elements. It is not known whether the testes may be stimulated directly under such circumstances through neuromechanisms independent of the anterior hypophysis. All types of male hypergonadism are extremely rare, with the exception of so-called familial or constitutional true hypergonadism. It is possible that there may be overproduction of either LH or FSH without overproduction of the other.

Rarely, adenomas and a variety of testicular tumors such as embryonal carcinomas and chorioepitheliomas may be associated with an increased production of testoids, folliculoids, and gonadotrophins.

**Clinical Picture.** As in the case of hypogonadism, the manifestations of hypergonadism vary with the age at onset.

**PREPUBERTAL HYPERGONADISM.** Leydig cell tumors or overgrowth of the testes with increased

secretion of testoids and rarely of folliculoids and gonadotrophins induce precocious puberty characterized by precocious development of all male sex characteristics. The term *precocious pseudopuberty* is often used to indicate the precocious development of Leydig cell function without seminiferous tubular cell function (fig. 120). This may

sive nitrogen retention induced by testoids is manifested by markedly increased muscular development and strength. This may result in the so-called "infant Hercules" type of appearance.

**POSTPUBERTAL HYPERGONADISM.** In this condition there is merely an accentuation of maleness, since the excessive androgen production occurs after skeletal development is complete. When the testicular tumor secretes an excess of folliculoids, feminization may take place, with gynecomastia a prominent manifestation.

**Diagnosis.** Diagnosis of male hypergonadism is suggested by the clinical features and by finding an increased urinary excretion of 17-ketosteroids and, rarely, of estrogens and gonadotrophin. In patients with normal testicular descent a tumor may be palpated in the scrotum. In the presence of cryptorchism it may be possible to palpate a tumor in the inguinal canal or by rectal examination.

**Differential Diagnosis.** Hypergonadism due to tumor or hypersecretion of testicular cells must be differentiated from adrenal masculinizing or feminizing tumors, thymomas, and tumors in and about the hypophyseal region.

True precocious puberty is characterized by early development of both seminiferous tubules and Leydig cells, in contrast to precocious pseudopuberty of testicular origin which is due in most instances to neoplastic proliferation of the testoid-producing Leydig cells. Hyperplasia of these cells may occur in conjunction with tumors or inflammatory lesions in the hypothalamic and diencephalic regions, with hydrocephalus due to distention of the third ventricle, or with pinealomas.

Constitutional hypergonadism, of genetic origin, is associated in the adult with increased activity of all elements of the testes. Excessive testicular development may also occur in the early stages of acromegaly and in other syndromes due to primary tumor of the hypophysis.

**Treatment.** The only known treatment is surgical removal or irradiation of the tumor. Effective removal of such a tumor should be followed by a return to normal in the urinary content of 17-ketosteroids, estrogens, and gonadotrophic substance. Early recurrence or metastases may be indicated by a rise in urinary gonadotrophin long before it is possible to detect the new growth by physical examination or roentgenography. Clinical evaluation may thus be aided by frequent urinary hormone assays.

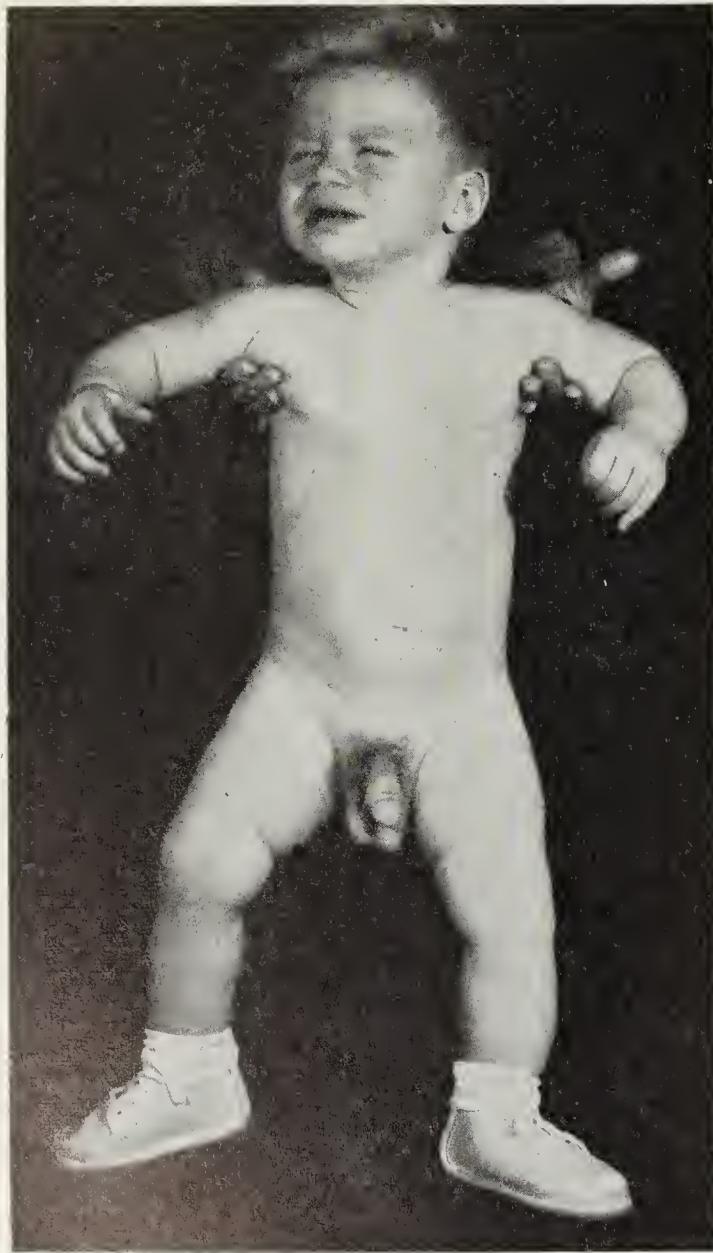


FIG. 120. Male, age seven months, in whom testicular biopsy showed precocious Leydig cell development.

lead to excessive growth of the penis with development of pubic and axillary hair, beard and mustache, deep voice, and excessive and precocious libido. Increased secretion of the sebaceous glands and acne are common. There is often a disproportionate skeletal growth, especially of the trunk, the arms and legs being comparatively short due to early epiphyseal closure. The excess-

### NEOPLASMS OF THE TESTES

Neoplasms of the testis are relatively uncommon. It is generally believed that they occur more commonly in the cryptorchid testis than in the normal testis. They may be classified as follows, listed in their relative order of frequency:

1. Teratocarcinoma
2. Seminoma (germinoma)
3. Embryonal carcinoma
- a. chorioepithelioma
4. Teratoma
5. Interstitial cell tumor
6. Fibroma, lipoma, adenoma, myxoma
7. Unclassified varieties

The incidence of teratocarcinoma is roughly constant throughout life, whereas the incidence of seminoma tends to rise with age. The immediate prognosis is very bad for embryonal carcinomas and chorioepitheliomas, somewhat less bad for teratocarcinomas and teratomas; whereas the immediate prognosis for seminomas is relatively good.

Endocrine changes such as gynecomastia and increased secretion of gonadotrophins giving a positive Aschheim-Zondek test are occasionally seen in chorioepitheliomas as well as in embryonal carcinomas and teratocarcinomas. The effects of interstitial cell tumors have been discussed.

**Diagnosis.** The diagnosis is made by palpating a mass, usually firm, smooth, and painless. Neo-

plasms must be distinguished from tuberculosis, usually hard and nodular; from syphilis, usually with a positive serologic test and a response to specific therapy; and from the various fluid-containing cysts (hydrocele, spermatocele) which usually transilluminate light. The diagnosis may also be aided by finding an increased urinary excretion of 17-ketosteroids, estrogens, or gonadotrophins, the latter giving a positive Aschheim-Zondek test. Rarely tumor cells may be identified in the semen.

**Treatment.** Surgical removal is always indicated in any tumor of the testis, and will usually effect a cure in the benign varieties. If the tumor is malignant, a radical operation followed by irradiation should be employed. Results of therapy may be followed by repeated determinations of the 17-ketosteroids or estrogens, or by the Aschheim-Zondek test, if originally positive.

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### Diseases of the Ovary

George W. Thorn and Peter H. Forsham

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**Introduction.** The ovaries possess ovulatory (reproductive) and hormonal functions, both of which are under control of the anterior pituitary gonadotrophic hormones. Abnormalities in ovarian hormone secretion frequently result in dis-

orders of menstrual flow, although it is apparent that not all abnormalities in menstrual flow are necessarily hormonal in origin.

**History.** The ovulatory and reproductive function of the ovaries was first described by a Dutch physician, Regner de Graaf, in 1673. He recognized small fluid blisters, now known as the Graafian follicles, which had succeeded in reaching the surface of the ovaries prior to ovulation. The hormonal functions of the ovaries were demonstrated in 1896 by the German biologist Knauer, who successfully reconstituted a sexual cycle in spayed animals by means of ovarian transplants. The presence of ovarian hormones in the follicles was demonstrated by R. T. Frank, and their occurrence in urine was established by the studies of Allen and Doisy, who demonstrated the effectiveness of potent urinary extracts in producing estrous changes in the vaginal mucosa of rodents. This relatively simple biologic assay method was an important step in the rapid isolation and synthesis of the ovarian steroids. In 1929 Doisy isolated estrone in crystalline form. The first total synthesis of an estrogen was that of equilenin by Bachman in 1939. Progesterone was identified and isolated by Allen and Corner, and was partially synthesized in 1934 by Butenandt and Fernholz.

**Physiology.** Sexual maturity in the human female is indicated by the onset of menstruation, the menarche, which normally occurs between the ages of 12 and 16 in this country. Menstrual flow concludes the regular occurrence of cyclical changes in the uterine mucosa approximately every 28 days. These changes are dependent upon normal ovarian function. Ovulation ceases at the menopause, which occurs as a rule between the ages of 45 and 55.

At puberty approximately 300,000 primordial follicles are scattered throughout each ovary; only a few of these mature and finally reach the surface of the ovary. Penetration of the ovarian surface is followed by the rupture of the follicle and liberation of the ovum into the peritoneal cavity. This phenomenon occurs approximately 14 days prior to the onset of menstrual flow. The ovum then finds its way into the Fallopian tube and is carried into the uterine cavity where it disintegrates within a few days unless it is fertilized in transit, usually in the peritoneal cavity, by a spermatozoon. Fertilization of the ovum is followed by the implantation of the fertilized

ovum in the uterine mucosa following which a placenta develops.

The maturation of the Graafian follicle is dependent upon the anterior pituitary follicle-stimulating hormone (FSH) which leads to the proliferation of the granulosa cells and the production of follicular fluid surrounding the ovum (fig. 121). The secretion of estrogens by the theca interna cells is stimulated by the anterior pituitary hormones, FSH and LH (luteinizing hormone). Together these hormones stimulate the growth and differentiation of the cells left behind after the escape of the ovum from the Graafian follicle, to form the corpus luteum, a richly vascularized body composed of steroid secreting cells. In conjunction with LH and FSH, anterior pituitary corpus luteum-stimulating hormone or CLSH (also called luteotrophic hormone or LTH) (prolactin) stimulates the secretion of progesterone by the corpus luteum during the two weeks of its existence for the latter half of the normal menstrual cycle. This action of CLSH (prolactin) continues during the prolonged life cycle of the corpus luteum of pregnancy, if fertilization of the ovum takes place, and supplements a similar action of the chorionic gonadotrophic hormone (CH). The latter is responsible for the positive pregnancy test.

Under the influence of estrogenic steroids the uterine mucosa undergoes proliferation and, with the addition of progesterone, secretory as well as predecidual changes occur. Increasing vascular engorgement of the uterine mucosa with poor oxygenation coincides with a gradual decrease in estrogen levels. Just at the onset of menstrual flow, the secretion of pituitary gonadotrophins (FSH and LH) is markedly reduced as a result of the inhibition of the pituitary induced by the increasing titer of circulating progesterone. The fall in pituitary gonadotrophin is followed by an abrupt cessation of estrogen and progesterone production and, in turn, by a complete termination of the already subliminal action of these steroids on the uterine mucosa. This interference with normal metabolic processes in the mucosa leads to a liberation of a necrotizing toxin which further enhances the breakdown and sloughing of the uterine lining. Hence a free menstrual flow is initiated which results in the physiologic, periodic shedding of the mucosal surface following failure of the ovum to be fertilized and implanted. The periodicity of the normal female

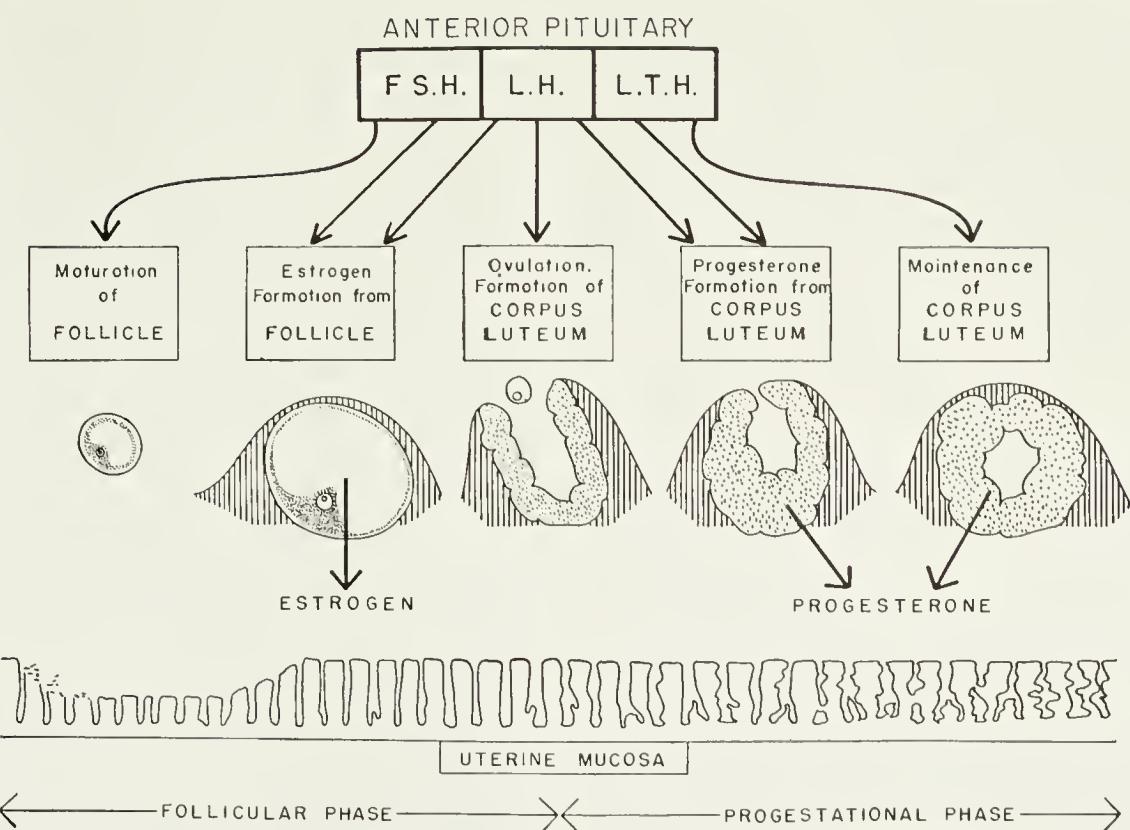


FIG. 121. Semidiagrammatic representation of the relation of anterior pituitary gonadotrophic hormones to ovarian and uterine changes during the menstrual cycle in normal women.

menstrual cycle is dependent upon the interaction of the anterior pituitary hormones stimulated through vegetative hypothalamic centers on the one hand and the ovarian estrogens and progesterone on the other. The pattern thus established is obviously subject to change with nervous, nutritional, and environmental stimuli as well as with local pathologic conditions.

**Ovarian Hormones.** Ovarian hormones are steroids. The estrogens (fig. 122) are characterized chemically by the presence of a benzene ring and a phenolic hydroxyl group which makes them soluble in alkali, a property used in their chemical separation. *Estradiol* appears to be the most potent naturally occurring estrogen and is known to be inactivated by serum and liver. A small portion is excreted as estriol or estrone in the urine, conjugated with sulfate or glucuronic acid. In small amounts estrogens stimulate the secretion of pituitary gonadotrophins, whereas larger quantities (more than 0.02 mg. of estradiol) will inhibit pituitary gonadotrophin secretion. The action of estrogens on the uterine mucosa has been discussed. The vaginal mucosae, and for that matter the oral and probably other mucosae, undergo cyclic changes in cytology related to alternating peaks of estrogens and progesterone. This forms the basis of the use of vaginal smears

in following the menstrual cycle, a somewhat unsatisfactory procedure in humans. The breasts show proliferative changes before the onset of the menstrual flow, dependent upon the combined action of estrogens, progesterone, and anterior pituitary prolactin. Estrogens in physiologic dosage will favor the rapid growth of breast cancer, whereas in very high dosage suppression and regression is often obtained. Uterine myofibromas are stimulated to growth by estrogens. Osteoporosis follows estrogen deficiency. Estrogens favor sodium and water retention.

*Undesirable effects* from estrogen administration include a painful, acute hepatitis with large doses; bone marrow inhibition and anemia; gastric irritation and typical morning sickness in some patients; as well as uterine bleeding when administration is stopped or when the dosage is suddenly reduced. The possible carcinogenic activity of estrogens calls for periodic and frequent checks of the breasts and genital tract of women on such therapy.

*Progesterone* (fig. 123) bears a striking resemblance to desoxycorticosterone. It has some sodium-retaining effect. It is actively metabolized by the liver, and a small fraction appears in the urine as the inactive pregnanediol (fig. 123), whence it may be isolated as the glucuronide.

At least 10 mg. a day should be present if a normal corpus luteum, the source of this hormone, exists. Along with its progestational activity, progesterone decreases uterine motility and acts as a central nervous depressor agent of considerable anesthetic value. There are no undesirable side effects from progesterone other than the salt and water retention and anesthetic effect in large doses.

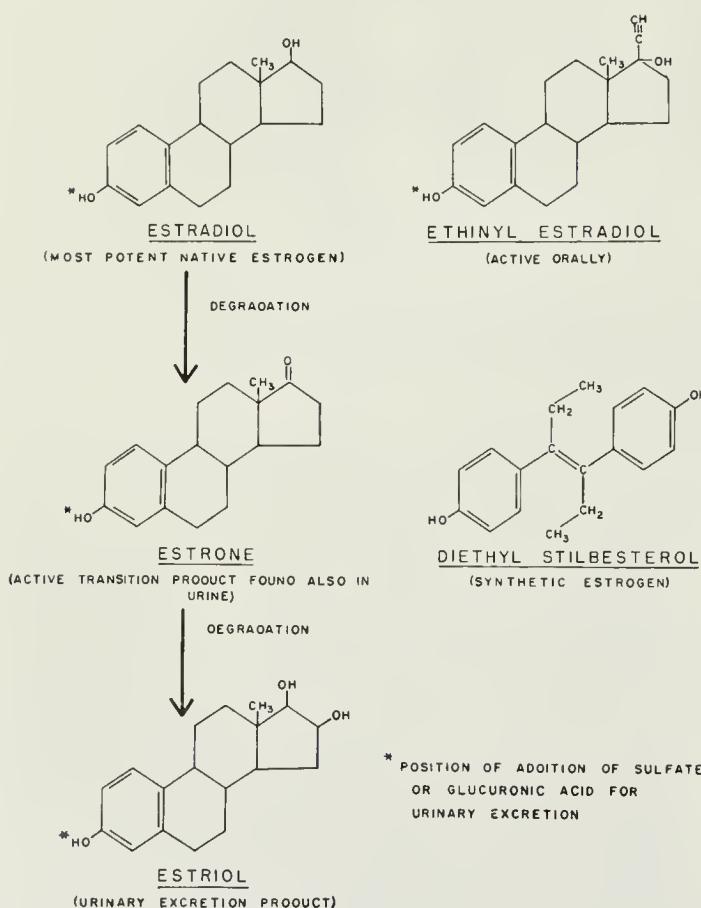


FIG. 122. Common estrogens.

OVARIAN PREPARATIONS FOR CLINICAL USE. Three general types of estrogens are available (fig. 122):

1. The naturally occurring estrogens related to estradiol, the most important natural estrogen. These substances cannot be given by mouth, and thus have restricted therapeutic usefulness.

Estrone sulfate isolated from pregnant mare urine may be given orally and does not induce gastric irritation. Such preparations are given in doses ranging from 0.625 to 10 mg. per day.

2. Ethinyl or vinyl estradiol. These potent preparations may be given by mouth and are devoid of gastric irritation. The dose of ethinyl estradiol is 0.05 mg.

3. Synthetic estrogens made up of two aromatic structures joined by a short aliphatic chain. The most commonly used preparation is diethylstilbestrol, potent orally but somewhat nauseating because of gastric irritation. Doses of 0.2 mg. per day will stimulate gonadotrophic function of the anterior pituitary, while larger doses will suppress it. Benzestrol and dehydrostilbestrol, related compounds, do not have the irritating effect.

Progesterone must be given by intramuscular injection in oil in doses ranging from 25 to 50 mg. per day (fig. 123).

Oral preparations retaining full activity consist of various progesterone derivatives such as anhydrohydroxyprogesterone (pregnenolone) used in the dosage of 25 mg. per day or more (fig. 123).

Estrogen and progesterone may be used together in order to reproduce the natural sequence of their appearance to induce anovulatory menstrual cycle.

## HYPOGONADISM

Hypogonadism is invariably accompanied by insufficient secretion of female sex hormones, by amenorrhea, and by incomplete development or maintenance of secondary sex characteristics.

## PREPUBERTAL HYPOGONADISM

This relatively rare condition is characterized by primary or lifelong amenorrhea. Pathologically there may be complete absence of the gonads or hypoplasia. With ovarian agenesis, skeletal

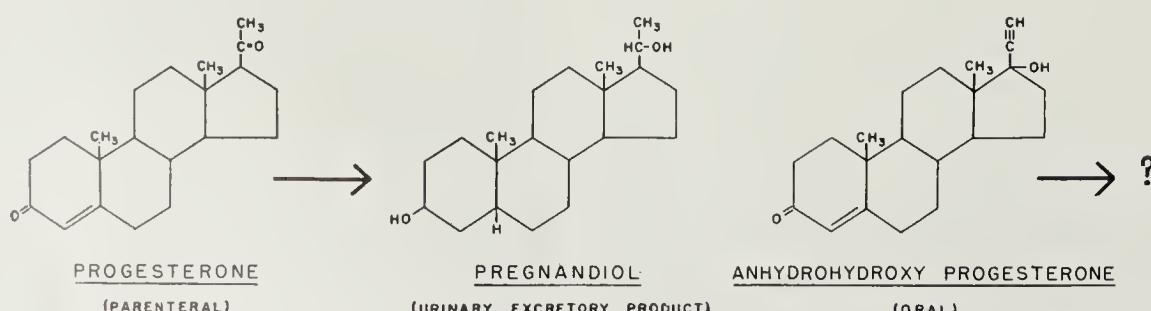


FIG. 123. Progesterone and derivatives.

growth is interfered with; whereas, with ovarian hypoplasia, there is overgrowth of the long bones which fail to close their epiphyses under the usual estrogenic stimulation during adolescence. If ovarian function is destroyed or impaired after birth but prior to puberty, there are no symptoms such as occur later in life in association with the climacteric or menopause. This apparently is due to the fact that increased autonomic activity resulting in stimulation of the anterior pituitary gland to secrete increased amounts of FSH does not occur prior to puberty.

#### PRIMARY OVARIAN INSUFFICIENCY

**Ovarian Agenesis.** Patients with this disorder present infantile sexual organs, complete lack of breast development, diminished axillary and pubic hair, and short skeletal stature, averaging 55 inches in height. Osteoporosis, delayed epiphyseal union, and precocious senility may also be observed. This condition is frequently associated with other congenital anomalies, such as webbing of the neck, cubitus valgus, horseshoe kidney, and cardiac abnormalities such as coarctation of the aorta (Turner's syndrome). All of these abnormalities appear to be the expression of a genetic defect, involving a varying number of genes, which impairs the function of the ovaries and vascular and skeletal development. Therefore, the clinical picture results from (1) genetic defects, of which ovarian agenesis is one, and (2) hormone deficiencies secondary to ovarian agenesis. The diagnosis is often made from the gross skeletal appearance of these patients. Urinary FSH titer is high, and the 17-ketosteroids are characteristically low but not absent, being derived almost entirely from the adrenal cortex in the female.

**Ovarian Hypoplasia.** In rare instances ovarian hypoplasia occurs. This condition is characterized by a failure of pubertal changes to occur and by delay in the closure of the epiphyses of the long bones. A marked increase in stature thus results which is accompanied by amenorrhea, underdevelopment of the breasts, and scant pubic and axillary hair. In this state there is no abnormal elevation of urinary FSH titer.

**TREATMENT.** Both ovarian agenesis and ovarian hypoplasia call for estrogenic replacement therapy, since there is no likelihood in the former, and little in the latter, of stimulating ovarian activity by trophic pituitary hormone therapy.

In both instances the dosage of estrogen should be kept low in the presence of ununited epiphyses in order to allow for optimal growth. This may be achieved by the daily administration of 0.1 mg. of diethylstilbestrol orally. Once the epiphyseal closure has occurred, larger doses of estrogens should be used, such as 0.3 to 0.5 mg. of diethylstilbestrol or 0.625 to 1.25 mg. of estrone sulfate. Withdrawal of estrogens every 24 days will usually result in a slight menstrual flow on the twenty-eighth day. This semblance of normal menstruation has no other than a psychologic usefulness. The supplementary use of 10 mg. of methyltestosterone by sublingual administration improves bone and muscular development and may lead to marked subjective improvement.

**Destructive Ovarian Lesions.** Destruction of the ovary by x-ray sterilization, surgical removal, tuberculosis, actinomycosis, and, in rare instances, pyogenic pelvic abscesses will preclude puberty and will require substitution therapy.

#### SECONDARY OVARIAN INSUFFICIENCY

**Gonadotrophic Hypopituitarism.** In this condition there is selective deficiency of gonadotrophic hormone secretion of the anterior pituitary, precluding normal ovarian development. Patients present amenorrhea, atrophic sex organs, and lack of breast development, with appearance of pubic and axillary hair at the time of expected puberty. There is usually some degree of osteoporosis. The characteristic hormonal changes include urinary FSH titer failing to show the usual prepubertal rise, without evidence of thyroid or adrenal insufficiency. The urinary 17-ketosteroid excretion is normal or slightly decreased.

**Panhypopituitarism.** These patients are dwarfs with no axillary hair. There are signs and symptoms of associated thyroid and adrenal cortical deficiency. Urinary FSH titer is very low or absent and the 17-ketosteroid excretion is characteristically decreased, depending upon the degree of involution of the adrenal cortex.

**TREATMENT.** Substitution therapy with pituitary gonadotrophin preparations, while therapeutically ideal, is not successful because of anti-hormones or antibody development to injections of protein hormones after three to six weeks of treatment. While there is little to be gained by such injections, they may prove helpful diagnostically. The treatment, therefore, is identical with that of primary ovarian insufficiency.

### POSTPUBERTAL HYPOGONADISM

This relatively more frequent disorder is characterized by estrogenic deficiency following (1) primary atrophy of primordial follicles; (2) destruction of the ovary resulting from disease of the ovary such as infection, trauma, x-ray treatment, surgical castration, etc.; or (3) ovarian atrophy secondary to gonadotrophic deficiency of the anterior pituitary gland. This estrogenic deficiency in turn leads to hypoplasia of the sex organs and loss of secondary sex characteristics, but without regression to the immature state.

It is apparent that the outstanding symptom of hypogonadism is amenorrhea; yet the diagnostic sign is the absence of ovulation, which, in turn, entails incomplete or insufficient ovarian hormone secretion. In arriving at the diagnosis of hypogonadism it is thus of prime importance to differentiate between anovulatory and ovulatory amenorrhea.

A record of daily basal oral temperature will reveal a sudden rise of approximately 1° F. at about the time of ovulation, which is indicative of progesterone production by the newly formed corpus luteum, since it can be reproduced at will by the administration of progesterone. The elevation in temperature persists up to one or two days prior to the menstrual flow, when a sudden drop occurs. The absence of such cyclical temperature changes suggests an anovulatory state. The method lacks complete reliability, however. Endometrial biopsy will allow the determination of cyclical changes in the uterus secondary to ovulation and corpus luteum formation. Chemical determination of urinary pregnanediol glucuronide, if found to be more than 10 mg. per day, indicates the presence of a functioning corpus luteum. Vaginal smears are not reliable for following the menstrual cycle.

### PRIMARY OVARIAN INSUFFICIENCY

In this condition, ovarian deficiency is associated with a normal anterior pituitary gland and the FSH titer is normal or elevated. Patients may complain of menopausal symptoms characterized by irregular menses or amenorrhea, irritability, nervous tension, vasomotor instability, hot flushes, hyperhidrosis, and weight gain. Hirsutism and osteoporosis are not uncommon. The latter are presumably due to a relative estrogenic insufficiency, whereas the vasomotor instability

is part of an overactive sympathetic discharge which probably accounts, together with low estrogen blood levels, for the elevated FSH secretion by the anterior pituitary gland.

**Polycystic Ovary (Stein-Leventhal Syndrome), Fibrocystic Ovary.** In this not uncommon disease of young women, the ovaries are filled with small cysts and atretic follicles and are invested by a thickened, fibrotic capsule making normal ovulation impossible while the uterine mucosa persists in the proliferative state. Clinically there are menstrual irregularities both in period and duration, culminating frequently in amenorrhea, dysmenorrhea, a tendency to obesity, slight hirsutism, and a pasty skin, in the absence of any marked abnormality in basal metabolic rate. There are no menopausal symptoms, and there is normal breast development. The picture might be accounted for in part by an elevated LH secretion of the anterior pituitary, stimulating ovarian androgenic rests.

**TREATMENT.** Medical therapy rarely leads to the re-establishment of normal ovulatory cycles. Surgery is indicated and consists of bisection and eversion of both ovaries after making certain that the Fallopian tubes are patent by air insufflation or "Lipiodol" roentgenograms. Normal ovulation will occur from the everted surfaces of the ovaries occasionally, but more often for periods of only a few months when another thick capsule is formed over the everted ovary. Treatment does allow for the possibility of a patient undergoing pregnancy, however. It is obvious that, with the primary cause not fully understood, treatment is in the empirical stage.

**Early Menopause (Depletion of Primordial Follicles).** This state is characterized by the premature occurrence of amenorrhea after less than the average span of normal menstrual cycles. The onset of the female climacteric before the age of 45 is definitely abnormal and probably related to an early depletion of primordial follicles. Apart from precluding conception, the knowledge of which may lead to serious social and psychologic difficulties in a young woman, the characteristic menopausal symptoms with their vasomotor instability may seriously handicap an otherwise normal individual.

**TREATMENT.** Treatment includes general psychologic support, sedation, and estrogenic therapy directed at the suppression of the hypothalamico-autonomic syndrome of which the excess

FSH secretion is an indicator. This may be achieved by giving diethylstilbestrol, starting with 0.1 mg. per day and increasing the dose by 0.1 mg. daily until 0.3 to 0.5 mg. daily is reached and continued. In this manner the gastric irritation accounting for some of the nausea associated with the use of this estrogen is minimized. Natural estrogens and synthetic derivatives which are non-nauseating may also be given. Thus 0.625 to 1.25 mg. of estrone sulfate or 0.05 mg. of ethinyl estradiol may be given by mouth daily.

**Female Climacteric or Menopause.** This condition usually arises between the ages of 45 and 50 years. In most instances there is a progressive irregularity in the frequency, duration, and amount of menstrual flow until only an occasional period or spotting occurs. This is followed by complete amenorrhea. Persistent metrorrhagia requires careful investigation. A recurrence of bleeding after a period of amenorrhea in patients over the age of 40 must be considered due to ovarian or uterine neoplasm until proved otherwise. This principle also applies to patients who continue to menstruate after the age of 50. The menopausal syndrome accompanying these changes in menstruation consists of emotional and vaso-motor instability of an autonomic nature. There is marked nervous tension and an often uncontrolled emotional expression with irritability. Vaso-motor instability is characterized by hot flushes and hyperhidrosis with drenching sweats alternating with chilliness. There is often a ravenous appetite, with rapid weight gain. Atrophic arthritis, indistinguishable from rheumatoid arthritis at times, but often superimposed upon the pre-existing hypertrophic type, occurs. Hirsutism and osteoporosis are not uncommon and are related to a relative estrogen deficiency. This syndrome gradually abates over a period of years, but in patients treated with estrogens these phenomena may return whenever treatment is discontinued.

**TREATMENT.** Substitution therapy is indicated, and a dosage similar to that outlined on page 639 may be employed. In contrast, however, to continued estrogenic therapy which is recommended in patients with early or premature menopause, estrogenic therapy should not be used indefinitely in the older age group. It is suggested that after a period of six months to one year of adequate treatment the estrogenic therapy be gradually decreased and finally discontinued. For

marked postmenopausal arthritis larger doses of estrogen (1 to 2 mg. of diethylstilbestrol or 3 mg. of estrone sulfate) are given. In using large doses of estrogen, care must be taken to examine the adnexa and breasts frequently because of the possible carcinogenic action. The possibility of utilizing pituitary adrenocorticotrophin or cortisone for short periods of time, if the arthritis is severe and disabling, should be considered. The dosage recommended is 10 mg. of ACTH every six hours, or 25 mg. of cortisone every six hours. Total treatment period should not exceed 21 days.

**Destructive Ovarian Lesions.** Destruction of the ovary by x-ray sterilization, surgical removal, tuberculosis, actinomycosis, and, in rare instances, pyogenic pelvic abscesses will lead to early menopause and will require substitution therapy.

#### SECONDARY OVARIAN INSUFFICIENCY

Since the regular occurrence of ovulation in the adult is dependent on the action of the hypothalamus on the anterior pituitary gland, the secretion of gonadotrophins by this gland, and their stimulation of ovulation, it is apparent that an abnormality at any one point in this chain may lead to amenorrhea.

Regardless of the cause, whenever amenorrhea is secondary to hypophyseal deficiency it is *not* associated with menopausal symptoms. Such patients merely evidence signs and symptoms of estrogenic deficiency and hypoplasia of the sex organs. The distinction between primary and secondary hypogonadism may be made on the basis of the absence of menopausal symptoms and an elevated urinary FSH titer. The absence of any pigmentary changes following administration of therapeutic doses of estrogens over a period of a month strongly suggests the presence of pituitary insufficiency. Conversely, primary hypogonadism will lead to menopausal symptoms and an elevated urinary FSH titer, and in such patients the administration of estrogens will lead to brown pigmentation of the linea alba, the areola, and the skin.

**Gonadotrophic Hypopituitarism.** In this syndrome, amenorrhea occurs as the only demonstrable deficiency related to pituitary function. The diagnosis and treatment are the same as those described on page 639.

**Panhypopituitarism.** In this condition, amenorrhea is usually an early sign of over-all pituitary insufficiency. The diagnosis and treatment are analogous to those given on page 639.

**Emotional, Psychogenic, or Hypothalamic Amenorrhea.** Emotional disturbances, through their influence on the hypothalamic centers controlling pituitary gonadotrophin secretion by a humoral mechanism, may induce amenorrhea. A history of emotional conflict is often obtained.

**TREATMENT.** Psychotherapy not infrequently restores normal menstrual periods. Since substitution therapy with pituitary gonadotrophins is impracticable because of antihormone formation, such cases must eventually be treated by estrogenic substitution therapy if symptoms related to the lack of estrogens are predominant. These symptoms include osteoporosis, hirsutism, and poor breast development. On occasion, anovulatory menstrual cycles must be induced in order to produce a semblance of normal events in a patient significantly depressed by the absence of normal menses.

**General Metabolic Disturbances Leading to Ovarian Insufficiency.** A number of profound metabolic disturbances and deficiency diseases are accompanied by amenorrhea presumably related to insufficient gonadotrophin secretion. Such diseases include anorexia nervosa, uremia, and uncontrolled diabetes mellitus, as well as hyperthyroidism. Simple obesity is often associated with amenorrhea.

**Masculinizing Syndrome.** Granulosa-cell tumors of the ovary and androgenic hyperplasia or tumor of the adrenal cortex may produce amenorrhea by suppressing pituitary gonadotrophins through an excessive secretion of androgens. Such causes are discovered by finding masses in either the ovary or the adrenal gland.

**TREATMENT.** After localization, surgical removal of the tumor is indicated, followed by local x-ray treatment in the case of granulosa-cell tumors. The special preoperative and postoperative procedures required for surgery on the adrenals is described on page 601.

#### HYPERGONADISM AND MENSTRUAL IRREGULARITIES

Excessive secretion of ovarian steroids will manifest itself either by initiating or by upsetting the cyclical changes of the normal menstrual cycle, while not noticeably altering established sec-

ondary sex characteristics. This may result in abnormal uterine bleeding, metrorrhagia (frequent bleeding), menorrhagia (excessive bleeding), or both. During the active reproductive period, phases of relative hypergonadism are exceedingly common, benign, and often transitory in nature. However, irregularity in the duration or frequency of menstruation necessitates thorough investigation of the cause. Any uterine bleeding before puberty and after menopause must be viewed with grave suspicion, since a malignant change is responsible for over 50 per cent of such occurrences in those age groups.

#### PREPUBERTAL HYPERGONADISM

Prepubertal hypergonadism is usually due to primary ovarian changes or, rarely, secondary to midbrain lesions and consequent premature increase in pituitary gonadotrophin production.

The occurrence of vaginal bleeding associated with breast development, the premature establishment of secondary sex characteristics, rapid skeletal growth, and an adult sexual drive make up the syndrome of "precocious puberty."

**Constitutional Sexual Precocity.** The onset of a menstrual flow before the age of 10 is unusual, but occurs on occasion in patients of Mediterranean origin.

**Albright's Disease.** A special form of polyostotic fibrous dysplasia is a congenital disease characterized by scattered fibrous bone lesions (osteitis fibrosa disseminata) and brown pigmentation, and is accompanied by sexual precocity.

**Granulosa-Cell Tumors of the Ovary Associated with Precocious Puberty.** This rare cause of precocious puberty is characterized by the syndrome of sexual precocity associated with what is usually a solid mass in one of the ovaries, varying in size from very small to very large. The uterine mucosa, which is often hyperplastic, always shows the proliferative picture characteristic of estrogenic activity. The malignancy of such tumors in childhood is remarkably low.

**Choriocarcinomatous Teratomas.** These are extremely rare tumors found in the ovaries of prepubertal females and growing to palpable size. Because of the elaboration of chorionic gonadotrophins, one occasionally finds uterine bleeding from a hypertrophic uterine mucosa.

The diagnosis is made from the presence of a palpable ovarian mass and a positive pregnancy test because of the high titer of chorionic gonado-

trophin. All reported cases have been fatal because of the extreme malignancy of this primary ovarian chorioepithelioma, and radical surgery followed by x-ray therapy holds the only hope for even short-time survival.

### POSTPUBERTAL HYPERGONADISM

Hypergonadism may be either primary, due to changes in ovarian endocrine activity, or else secondary, due to overstimulation of ovarian hormone production by pituitary gonadotrophins. As a rule, one is dealing with a deficiency in progesterone in the presence of normal or elevated estrogens. An anovulatory state exists. In the adult female, changes in the menstrual cycle constitute the only overt evidence of hypergonadism. Other causes of abnormal uterine bleeding must be considered and ruled out (table 71).

*Table 71*

#### CAUSES OF ABNORMAL UTERINE BLEEDING OCCURRING DURING THE CHILDBEARING PERIOD

##### DEFINITE CAUSES:

- Intrauterine tumors
- Infections of uterus or adnexa
- Pathologic pregnancy
- Retained products of gestation
- Submucous fibroids
- Abnormalities in blood clotting
- Estrogenic ovarian tumors
- Ovarian dysfunction

##### OCCASIONAL CAUSES:

- Myometrial and subserous tumors
- Pelvic inflammation
- Endometriosis
- Retroversion of uterus

**Amenorrhea or Oligomenorrhea.** The absence or paucity of menstrual flow is the manifestation of a temporary and intermittent, persistent follicular phase of the uterine mucosa, representing a continuous proliferation without any intercurrent mucosal breakdown. The diagnosis is established by finding follicular endometrium on biopsy.

**Metropathia Hemorrhagica.** Metropathia hemorrhagica or functional uterine bleeding may make its appearance as metrorrhagia (frequent, irregular menstruation with short intervals) or menorrhagia (excessive amounts of flow at regular intervals). In hyperfolliculoidism of this type, myofibromas of the uterus and chronic cystic

mastitis occur with comparative frequency.

**DIAGNOSIS.** The diagnosis requires the elimination of causes other than one of hormonal imbalance, as outlined previously in table 71, including a thorough pelvic examination after the age of puberty. The Papanicolaou smear of uterine secretions will, by showing any abnormal cytology, be a useful adjunct in the diagnosis of neoplasm of the uterus, cervix, vagina, or vulva, especially after menopause. Pregnancy will be revealed by a positive pregnancy test in most instances, although ectopic pregnancies often fail to show an increase in chorionic gonadotrophins. The possible effect of estrogenic substitution therapy must be inquired into, and such therapy may cause irregular bleeding in an individual patient whenever more than 0.5 mg. of diethylstilbestrol or 1.26 mg. of estrone sulfate is used in daily doses. Diffuse brown pigmentation of the skin with a darkened linea alba affords a valuable sign of such overdosage in the presence of adequate gonadotrophin production by the anterior pituitary gland. The absence of ovulation may be demonstrated either by finding no basal temperature changes or by demonstrating the presence of hyperplastic, proliferative endometrium in uterine biopsy at the time of an expected period.

Four common gynecologic conditions with an endocrine background must be considered in the differential diagnosis of functional uterine bleeding.

*Midcycle bleeding* associated with ovulation may occur. It is painful at times (*Mittelschmerz*), and associated with light staining. No treatment is necessary.

*Premenstrual tension* and *dysmenorrhea* are often accompanied by menstrual irregularities and premenstrual staining. Symptomatic therapy for dysmenorrhea, low back pain, and other types of distress should be applied, together with smooth-muscle relaxants related to atropine in their action. Dietary sodium restriction and administration of 4 to 6 Gm. of ammonium or potassium chloride daily will tend to reduce troublesome premenstrual edema. An attempt at stimulating the cyclic uterine changes by hormonal substitution therapy often affords relief. Small amounts of methyltestosterone, 10 mg. per day by mouth, may be helpful, presumably by reduction of uterine engorgement through suppression of the anterior pituitary gonadotrophins. In intractable

cases, presacral neurectomy often affords complete symptomatologic relief.

*Endometriosis* is a common disease of nulliparous young women sometimes associated with acquired sterility, dysmenorrhea, and cramping during periods of irregular menses. Adherent flow plugs of uterine mucosa are located around the large bowel, the adnexa, and most commonly the ovaries, and participate in the cyclic mucosal changes induced by ovarian hormones. Chocolate cysts are the characteristic lesion. Intraabdominal hemorrhages, local irritation, and adhesions result in dysmenorrhea and gastrointestinal disturbances.

The primary cause of this disease has variously been ascribed to displaced congenital rests of uterine mucosa, metaplasia of mesenteric tissue, or menstrual reflux with peritoneal implantation of the mucosal shreds.

Whichever the cause, treatment must aim at suppressing the irritative cyclical changes of the mucosal implants or at removing them from their mesenteric sites. Methyltestosterone administered in oral doses of 10 mg. twice a day will often suppress menstruation sufficiently to afford relief without giving rise to excessive signs of masculinization. Surgery, consisting of a panhysterectomy, should be reserved for only the most intractable cases.

*Myofibromas* of the uterus, representing a localized form of endometrial hyperplasia involving mostly the muscular layer, are stimulated to growth by estrogens. Occasionally, bleeding occurs from local trauma. The absence of any further growth of myofibromas at menopause points the way to rational therapy. This consists, in order of preference, of surgical removal, local x-ray therapy, or ovarian suppression with 10 to 20 mg. of methyltestosterone by mouth per day.

**TREATMENT OF FUNCTIONAL UTERINE BLEEDING.** In selected instances, *surgery* is the method of choice. This is hardly ever so before the age of 35, whereas surgery is to be considered invariably in postmenopausal bleeding.

Women between 35 and the menopause with functional bleeding, premenstrual tension, prolapse, and vaginal relaxation are best treated by complete abdominal hysterectomy, without removal of the ovaries. This procedure is preferable to simple sterilization by ovariectomy or by x-ray treatment of the region of the ovaries, since it removes sites for potential carcinoma, maintains

normal secondary sex characteristics, does not lead to the menopausal syndrome, and removes the chief focus of symptoms.

*Medical therapy* should be employed in the majority of cases of functional uterine bleeding between the ages of 15 and 35 once the functional nature of the disorder has been clearly established and other causes ruled out.

Three hypothetic cases covering the majority of instances of dysfunctional uterine bleeding follow:

**1. TREATMENT OF A PATIENT HAVING HAD A MENSTRUAL FLOW LASTING MORE THAN A WEEK.** Progesterone (25 mg. in oil) is injected intramuscularly daily for five days, or 20 mg. of anhydrohydroxyprogesterone by mouth is substituted. During this period of therapy the flow will diminish or cease. Two to four days after the end of therapy, a profuse menstruation will occur lasting less than six days, as a rule. The same treatment should be repeated 18 to 20 days after the first day of the induced flow. Normal cycles are likely to follow two or three of such progesterone series. Failure to obtain normal cycles calls for further investigation under anesthesia, in search for another cause of the uterine bleeding.

**2. TREATMENT OF A PATIENT HAVING PROFUSE BLEEDING AT NORMAL INTERVALS.** Beginning with the onset or after the first two days of menstrual flow, estrone sulfate (2.6 mg. three times a day by mouth) or, to reduce the expense, diethylstilbestrol (5 or 10 mg. in a glass of milk on retiring) is taken for 25 days. Two to six days after cessation of therapy, uterine bleeding will begin. Should early excessive flow appear again, the same treatment may be repeated. Both agents may cause either a sense of well-being or one of malaise, depending on the patient's unpredictable reaction. Diethylstilbestrol, unlike estrone sulfate, often produces gastric discomfort and nausea, which may be reduced by giving it with milk and by beginning the administration with 0.1 mg. and doubling that dose progressively while giving it four times a day. The occurrence of bleeding between the sixth day and the end of estrogen therapy indicates the presence of some undiagnosed uterine disturbance and calls for further investigation. Progesterone therapy may also be used between the eighteenth and the twenty-first day of the cycle. A profuse catamenia will result, but is usually of shorter duration than that obtained by estrogen therapy, and the re-

establishment of a normal cycle is more likely to result.

**3. TREATMENT OF A PATIENT HAVING MENSTRUAL PERIODS AT SHORTENED INTERVALS WITH OR WITHOUT EXCESSIVE FLOW.** Either the progesterone series is begun eight days before the onset of the expected premature period, or the estrogen therapy is given at the start of the flow. In both instances, bleeding following a progesterone menstruation or during estrogen therapy is indicative of further uterine disease.

A form of therapy applicable to all three varieties of functional bleeding consists of one injection of a crystalline suspension of 10 mg. of estrone and 50 mg. of progesterone about one week preceding the desired day of flow. This is repeated monthly until a spontaneous rhythm is re-established.

### FUNCTIONAL NEOPLASMS OF THE OVARY

Relatively few of the many known ovarian neoplasms are functional. They may be either male- or female-directed, and the struma will secrete thyroid hormone on occasion.

### ARRHENOBLASTOMA

Arrhenoblastoma is a very rare masculinizing tumor found predominantly in women between the ages of 20 and 30, and arising from male-directed cells of the ovary.

**Pathology.** Firm masses with occasional cystic degeneration of varying degrees of differentiation characterize this tumor. Strands of primitive cells are arranged in increasingly tubular fashion as the degree of organization increases. Sections often reveal interstitial cells known to secrete androgens.

**Clinical Picture.** Masculinization occurs, with a deep voice, hirsutism, small breasts, an enlarged clitoris, and nearly always amenorrhea. Pelvic discomfort is associated with a palpable mass. The tumor may be small or large, is usually freely movable, and not infrequently malignant.

**Diagnosis.** The clinical picture strongly suggests the presence of a masculinizing tumor. The finding of a normal 17-ketosteroid excretion distinguishes this tumor from the adrenogenital syndrome due either to adrenal androgenic hyperplasia or to the presence of masculinizing rests in the adrenal gland. A distinction between arrhenoblastoma or a luteoma could be made only at operation.

### LUTEOMA

Luteomas are a group of exceedingly rare tumors, usually benign, which may cause amenorrhea and some degree of masculinization in the presence of a secretory endometrium with pre-decidual changes.

**Pathology.** Most of these tumors are hardly distinguishable from adrenal cortical ones and are characterized by the occasional finding of corpus luteum-like cells.

**Diagnosis.** Masculinization, the presence of a mass, and low to normal 17-ketosteroids demand an exploratory operation.

**Treatment.** Surgical removal of the tumor is followed by complete return to normal.

### ADRENOCORTICAL-CELL TUMORS

Such tumors are manifested by masculinization and rarely reach palpable size. They represent adrenal cortical rests within the ovary and give rise to the adrenogenital syndrome on occasion. They are not malignant, so that simple surgical removal usually returns the patient to normal. As a rule, 17-ketosteroids exceed 30 mg. a day.

### GRANULOSA-CELL AND THECA-CELL TUMORS

These are a group of rare feminizing tumors. Whereas the granulosa-cell tumors are large, cystic, and often hemorrhagic, and are malignant in 30 per cent of the cases, theca-cell tumors usually form a firm mass and are benign.

**Pathology.** Cells of variable size make up a firm mass which may become cystic on occasion. Attempts at follicle formation known as Call-Exner bodies are diagnostic. The cells secrete estrogens and occasionally progesterone.

**Clinical Picture.** Precocious puberty in the child, menstrual irregularities in the adult, and postmenopausal bleeding in the aged lead one to suspect the presence of such tumors. At biopsy proliferative endometrium is present as a rule and, rarely, secretory changes are observed.

**Diagnosis.** The diagnosis is suggested by the finding of a tumor of the ovary with abnormal uterine bleeding, proliferative mucosa, and a low FSH.

**Treatment.** Surgical removal of the affected ovary is indicated, and, with a proven malig-

nancy, radical pelvic dissection is often necessary. Postoperative x-ray therapy should always be used for this x-ray sensitive tumor.

### CHORIOCARCINOMATOUS TERATOMAS

These are extremely rare tumors found in the ovaries of prepubertal females and growing to palpable size. The elaboration of chorionic gonadotrophins leads to occasional uterine bleeding from a hypertrophic uterine mucosa.

**Pathology.** The tumors, of various size, are made up of chorionic epithelium.

Table 72

#### NEOPLASMS OF OVARY\*

##### TUMORS ARISING FROM COELOMIC EPITHELIUM (VAGINAL, ENDOCERVICAL, ENDOMETRIAL, ENDOSALPINGIAL):

- Cystadenoma (endometrioma, endosalpingioma, adenoma, fibroadenoma)
- Papillary cystadenoma
- Malignant papillary cystadenoma
- Solid carcinoma

##### TUMORS ARISING FROM PRIMITIVE MESENCHYME:

- Arrhenoblastoma†
- Granulosa-cell, theca-cell†
- Luteoma†
- Dysgerminoma
- Fibroma
- Sarcoma

##### TUMORS ARISING BECAUSE OF CONTINUITY:

- Adrenal cell†
- Kidney-cell (hypernephroma)
- Mesonephroma
- Brenner (renal pelvis, ureter, or urethra)

##### TUMORS ARISING FROM OVA:

- Teratoma, chorioepithelioma,† struma†
- Dermoid cyst

##### METASTATIC TUMORS:

- From uterus (endometrial)
- From stomach (Krukenberg)
- From intestine (small or large), eye, rectum, breast, bile duct, etc.

\* From J. V. Meigs: *New England J. Med.*, **228**:53, 1943.

† Only these six are endocrinologically active.

**Diagnosis.** An ovarian mass with a positive pregnancy test in a prepubertal female establishes the diagnosis.

**Treatment.** Radical pelvic surgery and x-ray treatment are essential, since the disease has spread fatally in all known instances.

### NONFUNCTIONAL NEOPLASMS OF THE OVARY

The presence of an ovarian lesion, usually a fibroma, but on occasion a carcinoma, often manifests itself by a concurrent pleural effusion (Meigs's syndrome). The finding of pleural fluid on physical examination or by x-ray should lead one to suspect ovarian disease whenever heart failure, liver disease, renal insufficiency, or thoracic neoplasm is absent.

A list of ovarian tumors which may be useful in differential diagnosis of ovarian masses is shown in table 72.

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## Infertility

George W. Thorn and Peter H. Forsham

Definition  
Etiology  
Diagnosis  
Treatment

**Definition.** Infertility may be defined as the inability to conceive in the course of normal sexual activity. From a clinical standpoint, the terms infertility and sterility are often used interchangeably to mean inability to reproduce. It is estimated that approximately 10 per cent of married couples are unable to reproduce. In planning medical management it must be borne in mind that either one or both partners may be at fault.

**Etiology.** Either congenital or acquired structural defects or any disturbance in the normal biologic equilibrium in any part of the male or female genitourinary tract through which the ova or spermatozoa must travel or survive may be responsible for infertility. Endocrine or physiologic factors play a very small role in the etiology of infertility, as opposed to pathologic, anatomic, psychologic, or educational factors. Psychologic and emotional disturbances may lead to prolonged azoospermia in the male and anovulatory cycles in the female, as well as to loss of libido and inadequacies of sexual intercourse. Coital difficulties may also occur as a result of dyspareunia from any cause, including infections and malformation or occlusion of the genitourinary tract and endometriosis. Primary ovarian or testicular deficiency may occur as a consequence of genetic defects or secondary to infections, toxicity, trauma, or neoplasia, or following x-ray or surgical castration. Secondary gonadal deficiencies usually follow anterior pituitary failure. The normal survival or production of either spermatozoa or ova may be prevented by a number of states such as hyperthyroidism or hypothyroidism, dietary insufficiencies, chronic diseases or debilitating states in general, and infections of the genitourinary tract. Occasionally, intrinsic abnormalities of the sperm or ova may be responsible for infertility.

**Diagnosis.** Responsible factors may be single or multiple in either one or both partners. There-

fore a complete history and physical examination of both partners are prerequisites for future diagnostic procedures. A very careful marital, gynecologic, and urologic survey should always be made. Particular attention should be given to the detection of nutritional, endocrine, or other metabolic disturbances, as well as to the presence of infection or its sequelae. Careful psychologic evaluation must always be carried out, and psychiatric consultation may often be required before a final diagnosis is made.

Routine hematologic, biochemical, bacteriologic, and urologic laboratory tests may reveal an obvious etiologic abnormality. Certain special tests are indicated, as follows:

- A. In both males and females:
  - 1. A urinary follicle-stimulating hormone determination may be done which, if elevated, points to primary gonadal disease.
  - 2. Thyroid function may be evaluated by determination of basal metabolic rate, serum protein-bound iodine, or radioactive iodine uptake.
  - 3. Urinary 17-ketosteroid determination may be of value in determining adequacy of adrenal or testicular function.
- B. In the male:
  - 1. An evaluation of the semen for volume, viscosity, chemical composition (especially hyaluronidase), and spermatozoa count, with special consideration of abnormal forms which should not exceed 20 per cent of the normal 60 million per milliliter, is required.
  - 2. Examination of a prostatic smear for gonorrhea or nonspecific inflammatory disease is also useful.
  - 3. A testicular biopsy may be indicated.
- C. In the female:
  - 1. A hysterosalpingographic examination, with a radiopaque substance, or tubal insufflation according to the method of

- Rubin, are of value in determining the patency of the genitourinary tract.
2. Ovarian function may be ascertained by daily basal temperature records, determinations of urinary pregnanediol excretion, vaginal smears, studies of cervical mucus, and endometrial biopsy.
  3. Spermatozoa insemination (Huhner test) may occasionally be of value.

**Treatment.** In the general examination obvious abnormalities may be found which can be treated. Detailed sex education of both partners should be provided. Surgery is indicated in anatomic abnormalities or in neoplasia of the genital tract. Fibrocystic ovaries may require surgical eversion for restitution of normal ovulation. Chemotherapy should be employed to combat infectious disease. Systemic disease must be eradicated, and proper nutrition must be maintained, with special reference to a high protein intake and supplementary vitamin substitution, including vitamin E. Competent professional assistance in correcting psychologic and emotional disturbances should be provided.

In most cases of aspermia or anovulation the prognosis is poor, and the patient should be advised accordingly. In cases of sterility, testosterone therapy has been employed with variable success (see Chapter 61, p. 632). In the female, anovulatory cycles due to pituitary deficiency often become ovulatory spontaneously or will revert in some cases following a few courses of cyclical substitution therapy with estrogen and progesterone (see Chapter 62, p. 639). In cases of deficient luteal function, progesterone substitution therapy in doses of 10 mg. in oil given intramuscularly daily, beginning with ovulation and continuing until the onset of flow or conception, will often prove beneficial. Gonadotrophin therapy is rarely of benefit, although its use is logical in the treatment of infertility due to hypopituitarism. The technic of administering gonadotrophic hormones is still experimental. Good results have been obtained, however, in a few cases by giving either pituitary or pregnant mare's serum gonadotrophin (200 to 500 I.U.) and chorionic gonadotrophin (200 to 500 I.U.) simultaneously every other day for 20 days, with

a rest period of 10 days to prevent antihormone action (see table 73). Antihormones and hypersensitivity to the protein hormone preparations frequently develop and should be watched for. Desiccated thyroid (U.S.P.) may occasionally be useful, even in the absence of hypothyroidism. The usual initial dose is 60 mg. per day and is increased gradually until the basal metabolic rate attains a level between plus 10 and plus 20; therapy is then adjusted to maintain the basal

Table 73

## GONADOTROPHIC HORMONES COMMERCIALLY AVAILABLE

## PRINCIPALLY FSH ACTIVITY

- I. *Pituitary Gonadotrophins:* Derived from animal pituitaries, in dry form, in 5 ml. vials containing 500 to 625 rat units, together with sterile diluent. *Dose:* 25 to 150 rat units, given by subcutaneous or intramuscular injection daily or three to five times a week.
- II. *Pregnant Mare's Serum Gonadotrophins:* In dry form, in 1 ml. vials containing 10 Cartland-Nelson units, together with sterile diluent. *Dose:* 20 Cartland-Nelson units every other day (1 Cartland-Nelson unit is equivalent to approximately 20 I.U.).

## PRINCIPALLY LH ACTIVITY

- I. *Chorionic Gonadotrophins:* Derived from pregnant human or mare's urine, in dry or liquid form, in 5 to 10 ml. vials containing 1000, 5000, or 10,000 I.U. *Dose:* 500 to 1000 I.U. intramuscularly every other day.

metabolic rate at this level. Low dose x-ray irradiation (total 250 to 300 r) of the pituitary and ovaries has occasionally been used with success in some cases of functional menstrual disorders with infertility, but its efficacy is not proven. It is possible in certain instances to increase temporarily the release of hormone from the anterior pituitary as a consequence of the inflammatory reaction to irradiation. However, it is important to realize that the ultimate effect of irradiation, if any change occurs, is *destruction* and *not stimulation*.

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## Miscellaneous Hormonal Disturbances

George W. Thorn and Peter H. Forsham

### Diseases of Thymus Gland

- Introduction
- Anatomy and Pathology
- Tumors of Thymus
- "Status Thymicolumphanticus"
- Relation of Thymus Gland to Myasthenia Gravis

### Diseases of Pineal Body

- Introduction
- Clinical Picture
- Treatment

### DISEASES OF THYMUS GLAND

**Introduction.** It is thought by some that the thymus should be classified as one of the glands of internal secretion. However, classic extirpation experiments in a variety of animals have given no conclusive proof of its endocrine nature, and certainly thymectomy in the human causes no recognizable clinical syndrome. There is no doubt that the thymus is a storehouse of essential body constituents which may be readily mobilized in times of stress. It would appear that the growth-promoting effects observed in rats following the administration of thymus extracts (Rowntree) could be accounted for by the rich content of essential nutrients which the extract contained. Thymus hyperplasia and atrophy are characteristically associated with a wide variety of clinical conditions. Although the exact function of this organ remains in question at present, recent studies indicating the involutionary effect on the thymus of adrenal hyperactivity suggest in part the mechanism for the great and rather sudden changes which may occur in the size of this organ.

**Anatomy and Pathology.** The normal thymus of infants consists of a well-defined cortex composed of closely packed masses of lymphocytes and a medulla. During the process of differentiation into cortex and medulla, Hassall's corpuscles, or concentric masses of cells, appear in the sheets of epithelial cells of the medulla. The gland is a thick, solid structure which in infants may occupy most of the anterior mediastinum. Later in life its size decreases, relatively. Involution is accompanied by replacement with adipose tissue. There exists a reciprocal relation between the size of the thymus and adrenal cortical activity—

the latter inducing thymic and generalized lymphoid atrophy, whereas adrenal cortical insufficiency is characteristically associated with thymic hypertrophy and generalized lymphadenopathy. It is probable that the so-called "accidental involution of the thymus" so characteristic of severe illness is mediated by the adrenal overactivity in response to stress.

**Tumors of Thymus.** Tumors of the thymus, or thymomas, are difficult to classify. They are usually encapsulated and a single tumor may contain many different stages of histologic differentiation. Tumors of the thymus may be adherent to surrounding organs, but distant metastases are rare.

**"Status Thymicolumphanticus."** It is well known now that adrenal cortical insufficiency is associated with thymus enlargement and generalized lymphadenopathy. It is possible that some cases of sudden death formerly attributed to "status thymicolumphanticus" were in reality deaths due to acute adrenal insufficiency. Recent studies also indicate that many of the sudden deaths previously attributed to thymic obstruction or "status thymicolumphanticus" were actually explained by congenital obstructive anomalies or inflammatory lesions of the trachea and larynx.

**Relation of Thymus Gland to Myasthenia Gravis.** Thymomas are observed not infrequently in patients with myasthenia gravis, and there is considerable evidence to suggest that the clinical course of patients with this disease may be improved by irradiation or removal of the thymus. This is particularly true in patients with thymomas. It is impossible to predict which patients will be benefited by thymectomy or irradiation of the thymus, and the natural tendency of the disease to remit spontaneously further confuses the picture.

Recently the administration of adrenocorticotrophin (ACTH) has been employed in an effort to induce thymic atrophy following stimulation of adrenal corticoid output. Variable success has attended this endeavor, the most favorable re-

port to date indicating no benefit, or possibly aggravation, during ACTH treatment, with improvement following cessation of therapy. It has been reported that thymus tissue from a patient with severe myasthenia gravis decreased the *in vitro* synthesis of acetylcholine.

It is apparent that the thymus, being composed of lymphoid tissue and containing a relatively high concentration of essential metabolites which may be mobilized rapidly, represents an integral part of the body's defense mechanism which is directly under hormonal control. To eliminate a hormonal function of the gland itself, under these circumstances, is difficult, although to date no convincing evidence of hormonal function has been adduced. Experiments carried out in the intact animal must all be controlled for the nonspecific pituitary-adrenal response to stress before the specificity of thymic response is established. Doubt also must be cast on the importance of thymomas as a cause of Cushing's syndrome on the basis of published reports, in view of the changes observed in other endocrine glands in these patients.

### DISEASES OF PINEAL BODY

**Introduction.** In 1898 Heubner described a case of precocious sexual and somatic development in a young boy who proved to have a tumor of the pineal body. Subsequently, in the next 10 years, 40 similar cases were collected by Marburg. However, with improvement in neurosurgical technic, it became evident that removal of the pineal body (Dandy) failed to cause demonstrable deficiency symptoms. Furthermore, the early reports of Rountree (1936) on the acceleration of sexual differentiation in rats following pineal extract therapy have not been confirmed by other investigators. It appears likely that pineal tumors cause endocrine disturbances, not by virtue of abnormal hormone secretion but rather by local pressure on the hypothalamic center and

the pituitary. There is no evidence to date to support the endocrine nature of the pineal body; there is, however, definite evidence of a clinical syndrome of macrogenitosomia precox (Pellizzi's syndrome) associated with tumors of the pineal body. It occurs only in boys; it is not observed in the rare pineal tumors in girls or in adults of either sex.

**Clinical Picture.** Precocious sexual development and skeletal growth are the most striking clinical manifestations. The sex glands attain adult size before puberty, and the skeletal growth and adult body proportions are strikingly precocious. Other signs of the tumor are related to local neurologic changes. It is important in any young male child with precocious development to consider the possibility of an intracranial tumor, particularly pinealoma. The clinical manifestations of these tumors may be duplicated in every detail by tumors of adjacent areas of the brain.

**Treatment.** Surgical removal is the only cure; cerebral decompression and irradiation offer only palliative relief.

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## Section 3—Metabolic Disorders of Bone

# 65

## General Considerations

Edward C. Reifenstein, Jr.

### Physiology of Bone

#### Calcium and Phosphorus Metabolism

#### Action of Parathyroid Hormone and of Related Sterols

#### Definition of Metabolic Bone Disorder

#### Classification of Metabolic Disorders

### PHYSIOLOGY OF BONE

From a metabolic point of view, adult human bone consists of a mass of protein tissue in which is deposited a calcium-phosphate-carbonate salt. This mass can be considered to have three surfaces: (1) a surface upon which nothing appears to be happening (which includes about 90 per cent of bone surface), (2) a surface upon which bone is being formed, and (3) a surface upon which bone is being resorbed. It should be noted that bone formation and bone resorption are going on at the same time side by side, and hence that the mass of bone is in a state of dynamic equilibrium.

The mass of bone is surrounded by body fluids which contain calcium and phosphorus ions. It is the interpretation of the author that the saturation of calcium ions  $\times$  phosphorus ions (i.e., the ion product) in the body fluids of the normal individual is such that bone is constantly being resorbed in accordance with physical-chemical laws in order to satisfy the solubility product (i.e., the ion product at which the solution is just saturated). At the sites of bone resorption are found large multinuclear giant cells called osteoclasts. According to various interpretations, these are either foreign-body giant cells cleaning up the debris, clumps of osteocytes after the inorganic salt has been removed, or cells identical with the osteoblasts (*vide infra*) which have a different histologic appearance and biologic activity because of their environment. Calcium and phosphorus are released from bone in a ratio by weight of 2.2 to 1, and the residual protein matrix disappears. This process is accelerated by an increase in the acidity of the body fluids, and

probably to a slight extent by a direct action of the parathyroid hormone (see Chapter 56); it is retarded by an increase in the alkalinity of the body fluids.

The universal tendency to bone resorption is thought to be offset at certain bone surfaces by the activities of single-nuclei cells called osteoblasts. These cells are presumed to have two functions: (1) to lay down a protein matrix or osteoid in apposition to already calcified bone, and (2) to elaborate an enzyme, alkaline phosphatase. This enzyme, by splitting organic phosphate compounds, releases phosphorus ions and builds up the saturation of calcium  $\times$  phosphorus ions along the matrix to the point where deposition of calcium phosphate occurs. Bone formation, therefore, consists of two steps: (1) the laying down of the matrix, and (2) the deposition therein of the calcium phosphate salt. In the absence of liver disease, the alkaline phosphatase level in the blood is thus an index of osteoblastic activity, and hence of bone formation. Calcium and phosphorus are deposited in the matrix of bone in a ratio by weight of 2.2 to 1. The site at which bone formation occurs depends upon the stress placed upon the bones, since the osteoblasts exhibit their physiologic activity in response to stress. Adequate amounts of protein foodstuffs, ascorbic acid, and estrogen are required for normal osteoblastic activity.

Three types of bone formation are found: (1) endochondral, (2) membranous, and (3) endosteal. In the first, bone formation takes place after a preliminary formation of cartilage; in the second, bone formation occurs in specialized mesenchymal tissues in the embryo without a preliminary cartilaginous phase; in the third, bone is formed by apposition to the cortex and trabeculae as part of the constant remodeling of bone. In the final analysis, all three types of bone formation involve essentially the same process—the laying

down of the extracellular matrix (osteoid), and the deposition into this osteoid of a calcium-phosphate-carbonate salt.

### CALCIUM AND PHOSPHORUS METABOLISM

The general aspects of the metabolism of calcium and phosphorus are discussed in Chapter 29 in connection with the alterations in the electrolyte composition of the body fluids.

### ACTION OF PARATHYROID HORMONE AND OF RELATED STEROLS

The action of the hormone of the parathyroid glands is described in Chapter 56 in relation to the alterations in calcium and phosphorus metabolism, and in Chapter 69 as part of the consideration of metabolic disorders. The action of Vitamin D (calciferol, Vitamin D<sub>2</sub>) is discussed in Chapter 68.

*Table 74*

SUMMARY OF ACTION OF PARATHYROID HORMONE, CALCIFEROL (VITAMIN D<sub>2</sub>), AND DIHYDROTACHYSTEROL (A.T. 10)

	<i>Calcium Absorption from Gut</i>	<i>Phosphorus Excretion in Urine</i>
Parathyroid hormone.....	0	++++
Calciferol (vitamin D <sub>2</sub> ).....	+++	+
Dihydrotachysterol (A.T. 10)...	+	+++

In addition, a word must be said about the action of dihydrotachysterol (A.T. 10). This sterol also exhibits the two actions that have been observed with parathyroid hormone and calciferol: (1) that of increasing the absorption of calcium from the gastrointestinal tract, and (2) that of increasing the excretion of phosphorus into the urine. Dihydrotachysterol holds an intermediate position between the other two, since it has more effect than parathyroid hormone but less than calciferol on calcium absorption, and since it has more effect than calciferol but less than parathyroid hormone on phosphorus excretion (see table 74). The present evidence indicates that almost all of the phosphorus that appears in the glomerular filtrate is reabsorbed in the renal tubules in the parathyroidless individual; parathyroid hor-

mone decreases the phosphorus reabsorption. Dihydrotachysterol and calciferol appear to have two influences that contribute to their effect on phosphorus excretion: (1) by acting on the renal tubules they decrease phosphorus reabsorption, and (2) by decreasing parathyroid gland activity they increase phosphorus reabsorption. The final observed action is the resultant of these two opposing influences. The first influence is greater than the second for dihydrotachysterol, and vice versa for calciferol; thus, dihydrotachysterol seems to have less effect on the parathyroid gland activity than does calciferol. These relationships are shown schematically in figure 124.

### DEFINITION OF METABOLIC BONE DISORDER

A metabolic disorder of bone may be defined as a disease of bone arising from a disturbance in the general metabolism of the body. Metabolic bone diseases, therefore, are generalized or systemic bone diseases. The factor which produces the bone disease must be recognized as influencing all of the bones of the body; however, it is not uncommon for some parts of the skeleton to respond with a more pronounced degree of disorder than others. For example, there may be generalized decalcification as part of the bone disease with hyperparathyroidism, and, in addition, there may be localized cysts and tumors. Similarly, all of the bones of the body may be affected by the loss of stresses and strains which leads to atrophy (osteoporosis) of disuse; however, the patient immobilized in bed who develops osteoporosis of his limbs uses his skull and mandibles as much as when he is up and about, and, hence, these bones do not manifest the bone disease. Likewise, estrogen deficiency affects all of the tissues of the body, including the bones; in spite of this, the vertebrae show the most marked osteoporosis and the skull is but rarely involved.

To be contrasted with the metabolic diseases of bone are the localized diseases of bone. The one essential feature in establishing that a bone disorder is localized is the finding of normal, uninvolved bone. At the same time it should be pointed out that localized bone disease may be very widespread. For example, Paget's disease of bone may involve 95 per cent of the skeleton, but a careful roentgenographic survey will disclose normal bone in some area with a sharp line of demarcation between it and the involved bone.

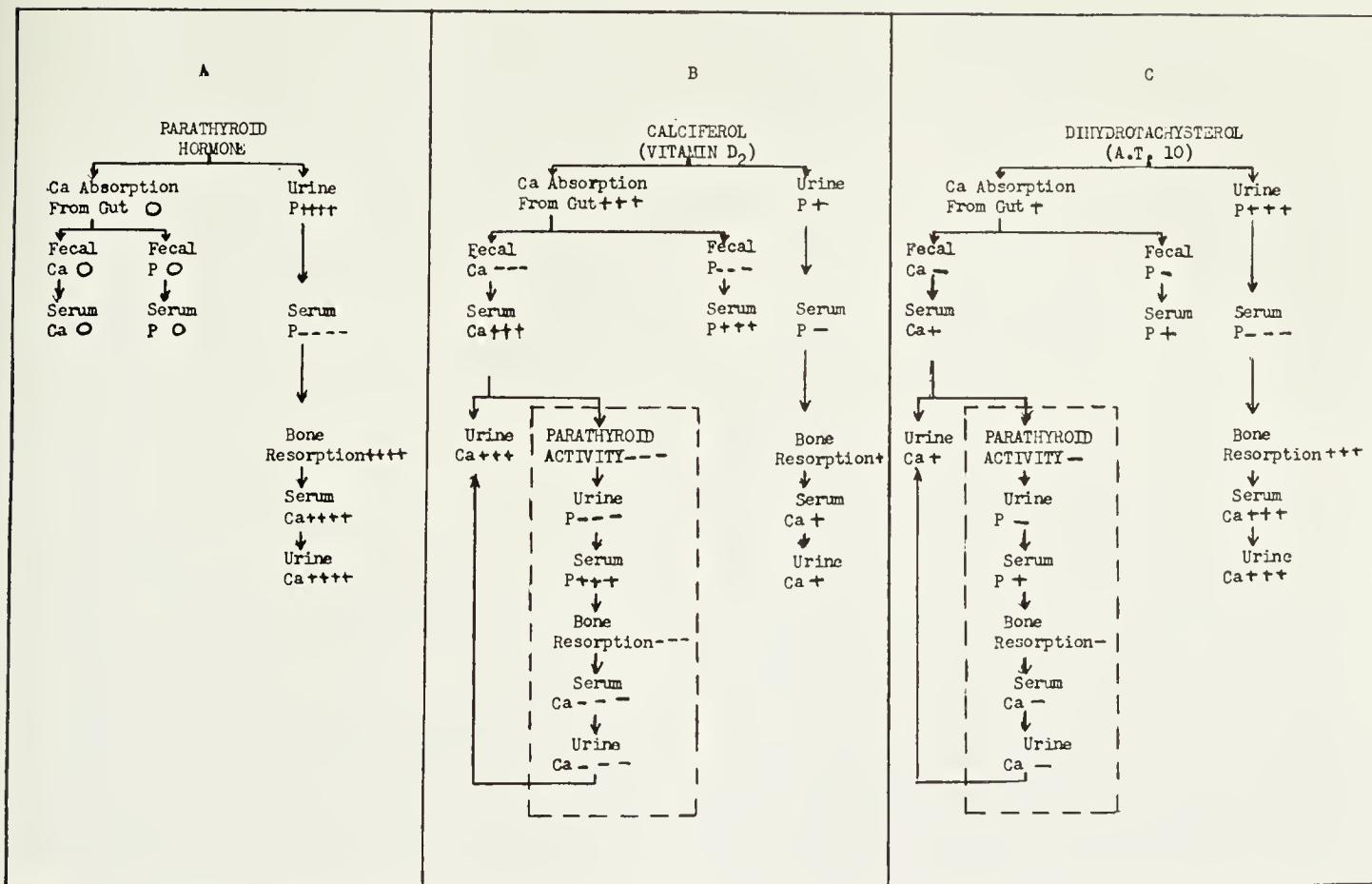


FIG. 124. Diagrams to illustrate the differences in the action of (A) parathyroid hormone, (B) calciferol, and (C) dihydrotachysterol. Note that the effect of parathyroid hormone is entirely on phosphorus diuresis while the effects of calciferol and dihydrotachysterol are on both calcium absorption from the gastrointestinal tract and on phosphorus diuresis. Note, furthermore, that calciferol has a greater effect on calcium absorption than dihydrotachysterol, while the dihydrotachysterol has a greater effect on phosphorus diuresis than calciferol. Thus, dihydrotachysterol resembles parathyroid hormone in its action much more than does calciferol. (+) Increased; (-) decreased; (0) unchanged.

## CLASSIFICATION OF METABOLIC DISORDERS

The metabolic bone disorders in adults can be divided into two main groups in terms of the total amount of calcified bone that is present in the body: there can be either "too-little-calcified-bone" or "too-much-calcified-bone." Since the mass of bone in the body is in a state of dynamic equilibrium, with bone formation and bone resorption going on at the same time, a decrease in the total mass of calcified bone in the skeleton can be brought about in two ways: either by changes in the amount of bone formation or by changes in the amount of bone resorption. Thus, one can have "too-little-calcified-bone" either because the bone formation is too little, or because the bone resorption is too much. Similarly, one can have "too-much-calcified-bone" because the bone formation is too great, or because the bone resorption is too little.

In table 75, metabolic bone diseases in adults

are classified according to this scheme. It will be noted that an even further subdivision is necessary, since bone formation consists of two steps: (1) the laying down of the matrix by the oste-

Table 75  
CLASSIFICATION OF METABOLIC BONE DISEASES IN ADULTS

- I. Too-Little-Calcified-Bone:
  - A. Bone-formation-too-little:
    1. Defect in matrix formation: Osteoporosis
    2. Defect in calcification of matrix: Osteomalacia
  - B. Bone-resorption-too-much:
    1. Osteitis fibrosa generalisata
- II. Too-Much-Calcified-Bone:
  - A. Bone-formation-too-much:
    1. Increased matrix formation: Elemental phosphorus poisoning, excessive stress, healed osteitis fibrosa generalisata, and healed osteomalacia
    2. Increased calcification of matrix: Nonexistent
  - B. Bone-resorption-too-little:
    1. Osteopetrosis
    2. Hypoparathyroidism

blasts, and (2) the deposition of the calcium salts into this matrix. Thus, there may be a defect in matrix formation or a defect in the calcification of the matrix, both of which would lead to too little bone formation, and, hence, to "too-little-calcified-bone." When the defect is in matrix formation, the condition is spoken of as "osteoporosis"; when the defect is in the calcification of the matrix, the defect is spoken of as "osteomalacia" (adult rickets). Too much bone resorption produces the condition called "osteitis fibrosa generalisata" which leads to "too-little-calcified-bone"; this occurs with "hyperparathyroidism" or with prolonged "acidosis."

Increased matrix formation should lead to too great bone formation, and, hence, to "too-much-calcified-bone." No very good example of this exists in clinical medicine. Excessive stress will result in a skeleton that is heavier than the average, but one cannot properly say that there is *too much* bone. Matrix formation may be increased excessively in local areas as with "elemental phosphorus poisoning" or with the excessive stress following degenerative arthritis of the hip ("*morbus coxae senilis*"). Increased activity of the osteoblasts in forming matrix may occur as a compensatory mechanism in some conditions with "too-little-calcified-bone," such as osteomalacia and osteitis fibrosa generalisata. The increased activity of the osteoblasts frequently persists for some time after the cause of the "too-little-calcified bone" has been eliminated; the net result is "too-much-calcified-bone." The evidence indicates that the matrix is either calcified or not calcified, and that it cannot become supercalcified; hence, there is no heading under "Too-Much-Calcified-Bone" which corresponds to "Osteomalacia" under "Too-Little-Calcified-Bone." "Too-much-calcified-bone" also results from too little bone resorption; examples are found in "Osteopetrosis" and "Hypoparathyroidism."

In this discussion, the terms "osteoporosis" and "osteomalacia" are used to indicate specific disease conditions, and not to describe any state of bone in which too little density is seen by x-ray. There is a tendency on the part of roentgenologists to call any bone which appears to have less than the normal amount of density, osteoporotic or osteomalacic. It is apparent from the previous discussion, however, that it is impossible to determine, from the amount of density present, whether the patient has osteopor-

osis, osteomalacia, or osteitis fibrosa generalisata. Furthermore, the early evidences of bone disease of any of these three types escapes recognition in the x-rays because it is impossible to detect with accuracy changes in density until at least 30 per cent of the calcium that has been present has been lost. Similarly, it is very difficult to detect recalcification by x-ray, because again a considerable amount of calcium must be regained before a recognizable increase in density can be observed in the x-ray films. Attention is called also to the tendency to use the term "decalcification," when the term "acalcification" is meant.

It should be pointed out that any bone which contains too little calcified mass may exhibit deformity. For example, deformities of the vertebra (codfish vertebra, wedged vertebra, crushed vertebra, and herniation of the nuclei pulposi into the end-plate of the vertebra) occur in osteoporosis, osteomalacia, and osteitis fibrosa generalisata, although they may be somewhat more common in osteoporosis. While it is true that some difference in the structure of the bone density may be detected by those experienced in interpreting x-ray films, greater assistance in diagnosis by x-ray can be derived from the location of the sites of predilection of the lesions. For example, osteoporosis commonly involves the spine and pelvis, and rarely the skull and extremities; osteomalacia frequently involves the extremities; osteitis fibrosa generalisata frequently involves the skull. Furthermore, the degree of involvement usually is greater in osteitis fibrosa generalisata and leads more often to an absence of the lamina dura in this condition. The occurrence of bone cysts and "brown tumors" in osteitis fibrosa generalisata, and of pseudofractures in osteomalacia, is of considerable diagnostic assistance. There is a greater tendency for bones to bend in osteomalacia, while spontaneous fractures are more prone to occur in osteoporosis and in osteitis fibrosa generalisata. All of these pathologic manifestations will be mentioned again in relation to the specific diseases; the point is that decreased density in itself has no particular diagnostic significance except to indicate that a metabolic bone disease is present.

## REFERENCES

- Albright, F., and E. C. Reifenstein, Jr.: "The Parathyroid Glands and Metabolic Bone Disease: Selected Studies," Baltimore, Williams & Wilkins Co., 1948.

## Osteoporosis

Edward C. Reifenstein, Jr.

### General Considerations

- Definition
- Clinical Types
- Postmenopausal Osteoporosis**
- Etiology
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- Pathology
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- Other Conditions Associated with Osteoporosis**
- Atrophy of Disuse
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- Osteoporosis and Hyperthyroidism
- Osteoporosis and Estrogen Deficiency States
- Osteoporosis of Old Age
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- Osteoporosis of Acromegaly
- Idiopathic Osteoporosis

### GENERAL CONSIDERATIONS

**Definition.** Osteoporosis is that category of "too-little-calcified-bone" in which the decrease of calcified bone tissue is due to inadequate bone formation because of insufficient production of bone matrix by the osteoblasts. Whatever matrix is formed is normally calcified. Thus, osteoporosis is primarily a disorder of tissue metabolism and only secondarily one of calcium and phosphorus metabolism, and the serum calcium and phosphorus levels are normal. Since the serum alkaline phosphatase level is an index of osteoblastic activity, one would, at first thought, expect it to be low. The value turns out to be normal, which is actually relatively low in view of the fact that the skeletal mass is greatly decreased, and hence more subject to the stresses and strains which usually stimulate the osteoblasts. The calcified mass of bone in osteoporosis decreases because bone resorption continues unabated, while bone formation practically ceases. In time, the bone mass becomes so depleted that the skeleton responds to the stresses and strains with a sufficient increase in osteoblastic activity and bone formation so that the bone mass, although reduced in quantity, is again restored to a dynamic equilib-

rium. Thus, in long-standing osteoporosis one does not find an increased amount of calcium excreted in the urine.

However, a different situation occurs when osteoporosis develops rapidly, as in the acute osteoporosis (atrophy) of disuse. Since bone formation decreases while bone resorption continues, hypercalcuria occurs, and may lead to the same kidney complications as are found in hyperparathyroidism, in which the hypercalcuria results from the hypercalcemia. In osteoporosis the degree of hypercalcuria, the diet being constant, depends on the discrepancy between bone destruction and bone formation. If osteoporosis develops gradually, this discrepancy is at no time great, and hypercalcuria is never marked. If, on the other hand, bone formation suddenly stops in a nonosteoporotic skeleton, or in a skeleton in which the turnover of bone is greater than normal (as in Paget's disease or in osteitis fibrosa generalisata with hyperparathyroidism), there is marked hypercalcuria.

**Clinical Types.** Osteoporosis has been encountered clinically in a number of conditions (see table 76): (1) in the postmenopausal state, and in other conditions where there is a deficiency of estrogen which is necessary for normal activity of the osteoblasts; (2) in atrophy of disuse, where the normal stimulus to osteoblastic activity is absent; (3) in malnutrition, where the bone matrix, like other protein tissues, has become depleted; (4) in scurvy, where the lack of ascorbic acid results in deficient formation of bone matrix as well as of protoplasm in general; (5) in hyperthyroidism, where the excessive utilization of protein for energy leads to deficiency of protein tissues, including bone matrix; (6) in old age, where all tissues (hair, skin, muscles) atrophy and there is atrophy of bone as well; (7) in Cushing's syndrome, where it is thought that excessive amounts of certain adrenal cortical hormones (those which lead to the conversion of protein to sugar) inhibit the anabolism of protoplasm, including bone matrix;

Table 76

## CLASSIFICATION OF CAUSES OF OSTEOPOROSIS

- I. Defect in Osteoblasts:
  - A. Loss of stress and strain:
    - 1. Atrophy of disuse
  - B. Lack of estrogen:
    - 1. Postmenopausal state
    - 2. Congenital hypoestrinism: Ovarian agenesis.
  - C. Congenital osteoblastic defect:
    - 1. Osteogenesis imperfecta
- II. Defect in Matrix:
  - A. Loss of androgen:
    - 1. Eunuchoidism
    - 2. ? Senile Osteoporosis
  - B. Loss of protein:
    - 1. Malnutrition
    - 2. Hypovitaminosis C
    - 3. Hyperthyroidism
    - 4. Cushing's syndrome
    - 5. "Alarm reaction"
- III. Defect Unknown:
  - A. Acromegaly
  - B. Idiopathic osteoporosis

(8) in the "adaptation syndrome" of Selye, where the pathologic physiology appears to be the same as in Cushing's syndrome; (9) in acromegaly, where the pathologic mechanism is not known, although it may be related to the increase of pituitary hormones or to the secondary lack of gonadal hormones; and (10) in idiopathic osteoporosis, where all of the previously mentioned conditions have been eliminated and the cause is still obscure. It is not uncommon for two or more factors to be present in the same individual. For example, women past the menopause who develop osteoporosis due to estrogen lack frequently are immobilized and then develop a superimposed osteoporosis of disuse. Similarly, a patient who has undergone an orthopedic operation may show osteoporosis from the combination of atrophy of disuse and the adaptation syndrome of Selye.

### POSTMENOPAUSAL OSTEOPOROSIS

**Etiology.** The major factor in the etiology, of course, is the loss of the estrogenic hormone with a consequent decrease in osteoblastic activity and inadequate bone formation. However, there seems to be another factor as well. The point is that all women after the menopause have an insufficient amount of estrogen for normal physiologic function of the uterus and, presumably, of the osteoblasts. Yet, only some of these women develop a clinical degree of osteo-

porosis. What is the factor that makes the difference? It may be related to the amount of calcium and phosphorus in the skeleton at the onset of the menopause, to diet, to physical activity, to the compensatory production of other hormones by the anterior pituitary gland or by the adrenal cortex, or to some other factor that is still completely obscure.

**Incidence.** Postmenopausal osteoporosis is the commonest form of osteoporosis, and also the commonest of all systemic osteopathies. A moderate degree is almost physiologic after a physiologic menopause. If all women over 50 years of age are carefully studied, about 10 per cent of them will be found to have clinical osteoporosis. The degree of osteoporosis increases with the duration of estrogen deficiency, and an artificial menopause leads to a more severe degree of bone disease than a physiologic menopause.

**Pathology.** Bone sections from patients with osteoporosis show a decrease in the calcified mass with very few osteoclasts and rare osteoblasts. The trabeculae are few and narrow. In the long-standing cases a small number of osteoid seams are seen which are of normal width. Grossly one observes spontaneous fractures, particularly of the vertebrae, with deformities.

**Clinical Manifestations.** Patients with postmenopausal osteoporosis complain of pain in the bones, particularly in the back; they show the deformities resulting from spontaneous fractures; they exhibit symptoms from renal calculi which have been developed during the acute manifestations of the disease; they have thin skin; and they exhibit weakness, anorexia, and manifestations of estrogen deficiency. Osteoporosis tends to involve the spine and pelvis and, rarely, the skull and extremities; there is a greater tendency to spontaneous fractures than to bending of the bones. It should be emphasized that there can be a great deal of deformity without any symptoms. This is particularly true of wedged and collapsed vertebrae. The condition is usually less serious than either the physician or the patient thinks. The tendency is to exaggerate the seriousness of these collapsed vertebrae and to immobilize the patient in a plaster cast for a long period of time, thus inducing atrophy of disuse which will increase the amount of osteoporosis.

**Diagnosis.** The cases of postmenopausal osteoporosis are differentiated arbitrarily by age

from senile osteoporosis in women: The cases which exhibit clinical symptoms before 65 are called "postmenopausal," and those after 65 are called "senile." To make the diagnosis, therefore, one looks for a patient under 65 years of age, with a history of natural or artificial menopause, with a pain in the back and x-ray changes which indicate decreased calcified bone mass, with normal serum chemistry, and possibly with a history of renal calculi, in whom all the other causes of osteoporosis can be eliminated, and in

whom there is a favorable response to therapy with estrogens and androgens.

**Differential Diagnosis.** (See table 77.) It has been pointed out that generalized demineralization involving the spine and the long bones occurs predominantly in osteoporosis, but it may be found occasionally in osteomalacia and in osteitis fibrosa generalisata. Both of these latter conditions are readily eliminated by the finding of normal values for the serum calcium, serum inorganic phosphorus, and serum alkaline phos-

Table 77  
CHEMICAL FINDINGS IN CERTAIN BONE DISEASES

Disease	Serum Calcium	Serum Inorganic Phosphorus	Serum Alkaline Phosphatase	Serum Total Protein	Urinary Calcium	Blood Acidosis	Generalized or Localized Bone Disease	Miscellaneous
Osteitis fibrosa generalisata (primary hyperparathyroidism)	H	L	H	N	H	0	G	..
Renal osteitis fibrosa generalisata ("renal rickets"; secondary hyperparathyroidism)	L or N	H	H	N	H	+	G	..
Osteomalacia with decreased calcium absorption (secondary hyperparathyroidism)	L or N	N or L	H	N	L	0	G	Steatorrhea
Osteomalacia with increased calcium excretion (secondary hyperparathyroidism)	L or N	N or L	H	N	H	+	G	..
Hypoparathyroidism	L	H	N	N	0	0	G	..
Osteoporosis	N	N	N	N	H or N	0	G	..
Osteogenesis imperfecta	N	N	N	N	N	0	G	..
Polyostotic fibrous dysplasia (osteitis fibrosa disseminata)	N	N	N or H	N	N	0	L	..
Paget's disease (osteitis deformans)	N	N	H	N	N or H	0	L	..
Multiple myeloma	N or H	N H or L	N	H	N or H	0	L	Globulin H; Bence-Jones protein +
Metastatic malignancy	N or H	N H or L	N or H	N	N or H	0	L	..
Xanthomatosis	N	N	N	N	N or H	0	L	..
Sarcoid	H or N	N	N	H	H	0	L	Globulin H
Vitamin D poisoning	H	H or L	N or H	N	H	0	G	..

G = generalized; H = high; L = low; L = localized; N = normal; 0 = absent; + = present.

phatase. An entirely similar picture by x-ray may rarely be found in multiple myeloma (Kahler's disease), and in these cases the blood calcium, phosphorus, and alkaline phosphatase levels also may be normal. The presence of an elevated serum protein level, of plasma cells in the peripheral blood or on bone marrow biopsy, and of Bence-Jones protein in the urine helps to confirm the diagnosis of multiple myeloma. Osteogenesis imperfecta occurs in young individuals with blue scleras, nerve deafness, and a family history of osteopathy. Metastatic malignancy, sarcoid, xanthomatosis, neurofibromatosis, Paget's disease of bone, and polyostotic fibrous dysplasia (*osteitis fibrosa disseminata*; Albright's syndrome) have characteristic localized x-ray changes, abnormal serum chemistry, or other distinguishing features which readily make it possible to eliminate them and to establish the diagnosis of osteoporosis.

**Prognosis.** The prognosis for patients with postmenopausal osteoporosis is relatively good since the disease is crippling, rather than killing. However, the disease requires prolonged treatment. The patients first treated in the series studied at the Massachusetts General Hospital have been under hormone therapy for over eight years, and only now are beginning to show unequivocal x-ray changes consistent with increased density of bone. The clinical response, however, is apparent in a few weeks and has been very striking. It will be discussed below.

**Treatment.** The therapy of postmenopausal osteoporosis can be divided into two portions: (1) the therapeutic program, and (2) the preventive program.

**THERAPEUTIC PROGRAM.** The most important medication for the therapy of this condition is some form of estrogen. For example, one can give orally "Premarin," 1.25 mg. three times a day for four weeks, skip seven days, and repeat. Or one can give injectable estrogens in equivalent dosage. It is important to emphasize that estrogenic medication should always be given intermittently. That is, the estrogen should be given for four weeks, and then stopped for a week in order to allow bleeding from estrogen withdrawal, and to eliminate overstimulation of the breast and uterus. Patients are instructed that there may be vaginal bleeding during the period when they discontinue treatment. However, they may not bleed for the first two or three

times that the medication is omitted. Patients are also instructed to report at once to the physician if they start to bleed at any other time; this enables him to keep a check on the development of any abnormal growth. The estrogenic therapy must be continued for a considerable period of time, at least for some years (see the Preventive Program below).

Second on the therapeutic program is the administration of some form of androgen. For example, testosterone "Lingusorbs," 6 mg. three times a day, can be administered for absorption through the buccal membranes of the mouth. Or testosterone suspension, 10 mg. twice a week, or testosterone pellets, 75 mg. every three months, can be injected or implanted. The androgenic therapy should be given continuously for at least 6 to 12 months.

The estrogenic and androgenic steroid medications have an effect upon extracellular fluid as well as upon the retention of protoplasm and bone. If edema develops, the first step is to reduce the amount of sodium in the intake. If this does not control the edema, then the patient should be given ammonium chloride or mercurial diuretics. Finally, if the edema persists after these measures have been tried, it may be necessary to reduce the steroid dosage.

There are other important points in the therapeutic program for treating patients with postmenopausal osteoporosis. They should eat a high-protein diet to provide materials with which they can build the protein matrix. They should take an adequate amount of water in order to avoid any tendency toward a concentrated urine when hypercalcuria is present. An excess of calcium or of vitamin D is to be avoided. These patients do not need extra calcium or vitamin D, as their primary need is for osteoblastic activity and for protein constituents. Furthermore, an excess of calcium or of vitamin D may aggravate the hypercalcuria and lead to renal calculi. Excessive immobilization must be avoided so that atrophy of disuse is not added to the causative factors for the osteoporosis. At the same time, it is desirable to provide some support for collapsed vertebrae, and the use of a corset or brace supporting these mechanically defective areas is worth while. It is also helpful to teach the patient the correct use of her muscles in order to avoid acute strain of the weakened back. It is necessary to bear in mind that these patients may have renal calculi,

and that these or the accompanying urinary tract infections may require therapy.

**PREVENTIVE PROGRAM.** Another phase of treatment deserves some comment. This might be called the preventive program. Since osteoporosis begins as soon as ovarian activity falls below the level at which normal function occurs, in other words, begins at the time of the menopause, the question is raised: "Should one treat patients after the menopause with estrogens prophylactically in order to avoid the development of clinical osteoporosis?" As has been indicated, by the time the clinical manifestations are apparent, or roentgenographic changes can be discerned, the damage has been done. Would it

not be better to treat all women after the menopause with estrogens in order to avoid this type of metabolic bone disease? This therapy appears to be indicated regardless of whether or not the patient has menopausal symptoms.

These considerations raise the philosophic question as to why women have menopause in the first place if it is so bad for them. The only answer that can be offered is a teleologic one. We have developed a race of women who cannot have children after reaching a certain age because it has been found that after that time they cannot produce satisfactory offspring. Thus, it is good for the race for a woman to have a menopause, but it is not particularly good for her.

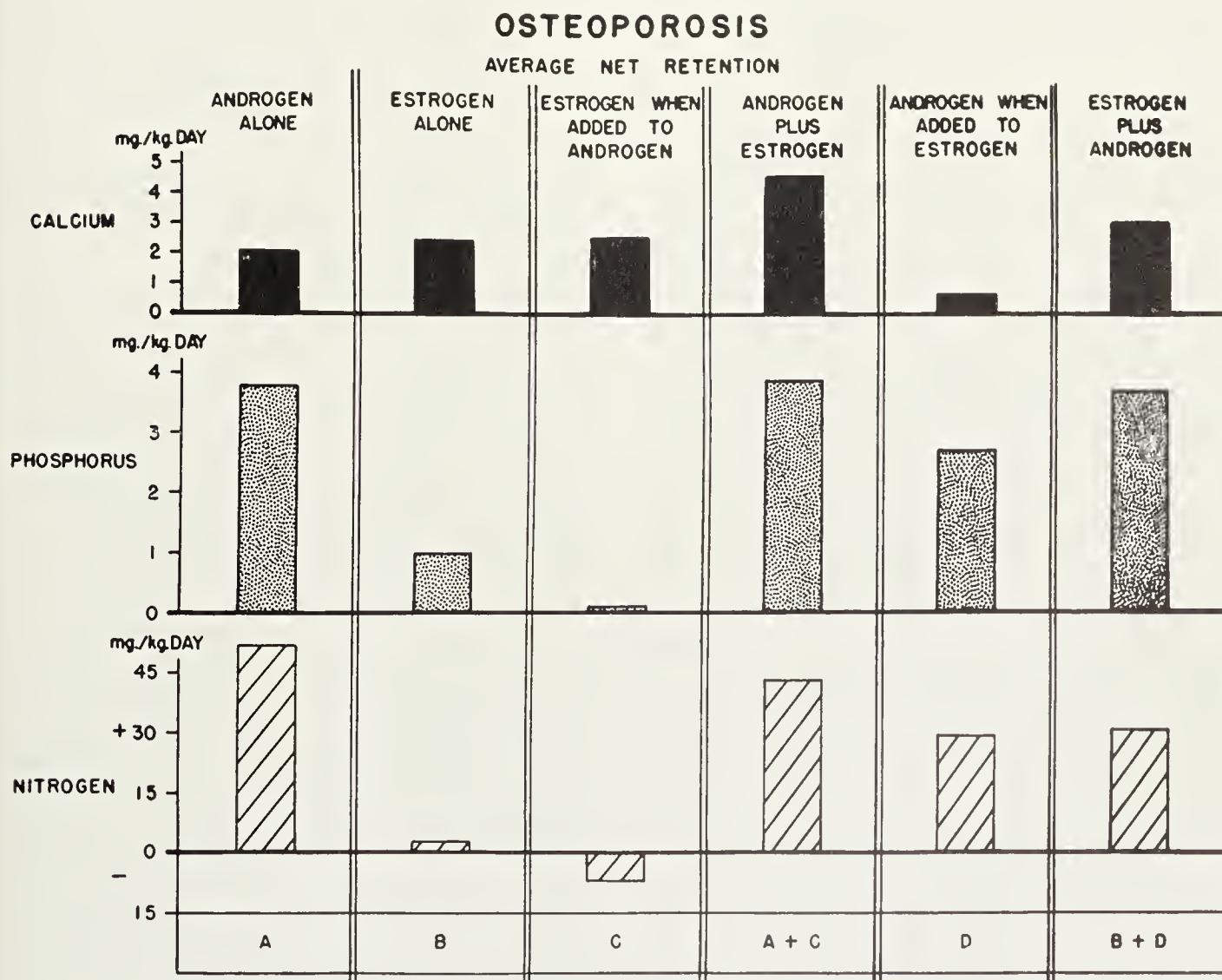


FIG. 125. Chart to illustrate the average net retention of calcium, phosphorus, and nitrogen with androgenic and estrogenic therapy by a group of patients with various types of osteoporosis during metabolic balance studies. Note that, when estrogen is given alone (B), there is a greater retention of calcium and a lesser retention of nitrogen than when androgen is given alone (A). Note that the additional effect of estrogen when given to a patient already receiving androgen (C) is retention of more calcium, while the additional effect of androgen when given to a patient already receiving estrogen (D) is retention of more nitrogen. Note that, while the combination of androgen plus estrogen (A + C) or estrogen plus androgen (B + D) does not result in as much nitrogen retention as androgen alone (A), both of the combinations result in a greater retention of calcium than either estrogen alone (B) or androgen alone (A).

**Results of Treatment in Clinical Studies.** The results of clinical studies employing the above therapeutic program indicate that a large number of patients with postmenopausal osteoporosis treated either with estrogen alone, or with a combination of estrogen and androgen, respond very well to this therapy. Pain in the spine and other bones is relieved considerably or completely in a matter of weeks to months. The body weight frequently increases, the skin appears to be thicker, the strength is increased, and the general well-being is much improved. Older women with fractures, particularly of the hip, respond especially well. These patients do better with the hormone therapy, as far as healing their bones and getting back on their feet are concerned, than they did without this type of therapy.

**Results of Treatment in Metabolic Studies.** A number of metabolic studies have been made on patients with various forms of osteoporosis. From them certain conclusions can be drawn. First, in regard to estrogen, estrogenic therapy decreases the calcium and phosphorus excretion in all types of osteoporosis except idiopathic osteoporosis. The fecal as well as the urinary calcium and phosphorus excretions are decreased in most cases. The effects of the estrogenic therapy are manifested within 6 days, are maximal in 30 days, and persist for 30 to 50 days after the therapy is stopped. The serum inorganic phosphorus, which tends to be high in postmenopausal cases, falls during estrogen therapy. The serum alkaline phosphatase does not rise, however, as one might have expected. The urinary nitrogen shows a poorly sustained decrease with estrogenic therapy. There is no convincing evidence that large doses are better than small.

As far as the therapy with androgen is concerned, this type of medication, like estrogen, produces a decrease in the calcium and phosphorus excretions in the types of osteoporosis studied. Furthermore, as with estrogen, the fecal as well as the urinary calcium and phosphorus excretions are decreased, the effects on calcium metabolism are slow to reach a maximum, and persist for a long period of time after the androgen administration is stopped. The serum phosphorus level tends to fall with androgen therapy, and the serum alkaline phosphatase does not rise except in cases of osteoporosis with Cushing's syndrome. However, unlike estrogen, androgen causes a decrease in urinary nitrogen excretion

which is marked and prolonged. Some studies have been made with progesterone, and it has been shown to produce no definite effects either alone or with estrogen.

In summary (see fig. 125), estrogen alone has a greater effect on calcium retention than androgen alone, whereas androgen alone has a greater effect on nitrogen retention than estrogen alone. However, regardless of whether estrogen is given in addition to a patient who has been receiving androgen, or androgen is given in addition to a patient who has been receiving estrogen, the combination of the estrogen and the androgen causes a greater amount of retention of calcium than either will produce alone. It is for this reason that the combination of estrogen and androgen is recommended in the therapeutic program.

#### OTHER CONDITIONS ASSOCIATED WITH OSTEOPOROSIS

The other conditions associated with osteoporosis have already been enumerated. Some additional points concerning these other conditions need to be mentioned.

**Atrophy of Disuse.** When a previously active portion of the skeleton is immobilized, as it may be by a plaster cast or by a flaccid paralysis, the normal stimulus of stress and strain is removed from the bone. As a result, the osteoblasts stop laying down matrix, and bone formation is greatly reduced. Since bone resorption continues unabated, in a relatively short time the skeleton loses a considerable amount of the calcium that was present. Some metabolic studies on normal young adults indicate that immobilization produces a loss of 1 to 2 per cent of the total body calcium in a period of five or six weeks. It should be obvious that atrophy of disuse rarely involves the skull, since a person lying in bed uses his skull almost as much as when he is walking. Similarly, the immobilized person uses his jaws in eating, and hence the lamina dura remains intact. Atrophy of disuse frequently complicates the other types of osteoporosis, and particularly those due to old age, the adaptation syndrome of Selye, and estrogen deficiency.

**Osteoporosis and Malnutrition.** The role of diet in osteoporosis is not exactly clear. It is quite obvious that, when the diet is inadequate in protein, insufficient amounts of protein tissue are formed in the body, and thus that the organic matrix of bone will not be formed in adequate

amounts, so that osteoporosis results. When the diet is inadequate in calcium and phosphorus, the condition that develops is osteomalacia rather than osteoporosis. There are some studies which suggest that diets high in calcium, phosphorus, and vitamin D have a beneficial effect on osteoporosis. However, there is no evidence that these minerals stimulate osteoblastic activity. Rather they tend to decrease the amount of resorption of bone, and this in itself would have some favorable effect upon the course of osteoporosis. Malnutrition probably plays a part in the osteoporosis observed in hyperthyroidism and long-standing, poorly treated diabetes mellitus; in these cases the prolonged use of protein for energy may result in a deficiency in some constituent of protoplasm which is needed for bone matrix formation.

**Osteoporosis and Hypovitaminosis C.** Ascorbic acid is necessary for the formation of the collagenous material of fibrous tissue structures, including the matrix of bone. Vitamin C deficiency in children results in a decreased osteoblastic activity, as is shown by the fact that the serum alkaline phosphatase level is decreased. Frank scurvy in adults is relatively rare, but is accompanied by typical osteoporosis. Deficiency of ascorbic acid also may be an important contributing factor in the osteoporosis due to malnutrition, hyperthyroidism, etc.

**Osteoporosis and Hyperthyroidism.** Osteoporosis does occur in patients with hyperthyroidism; it seems likely, however, that in this condition the cause is a combination of malnutrition and lack of vitamin C, since it is recognized that larger than normal amounts of protein substances and vitamins are required by patients with increased thyroid function. In the absence of an increased intake, excessive utilization of protein for energy may result in a deficiency of protein tissues, including bone matrix. The same explanation applies to osteoporosis associated with poorly controlled diabetes mellitus.

**Osteoporosis and Estrogen Deficiency States.** Osteoporosis due to estrogen deficiency occurs in the postmenopausal state which has already been discussed. There are other patients who are deficient in estrogen. Examples are the patients with the syndrome of ovarian agenesis, where the ovaries are congenitally atrophied; those with panhypopituitarism, in whom there is inadequate stimulation of the ovaries and, as a

result, inadequate estrogen production; and those patients with a selective lack of pituitary gonadotrophic hormones to stimulate ovarian estrogen production. When this estrogen deficiency is sufficiently long standing, one observes the same manifestations of osteoporosis as one sees in the postmenopausal patient. Many of these patients exhibit, as an early manifestation of the estrogen deficiency, a delayed union of the epiphyses which has been called "epiphysitis."

**Osteoporosis of Old Age.** It is recognized that all tissues atrophy with age; bone is no exception, and the skeletal atrophy is termed "osteoporosis." It is not known how much of the atrophy of old age is due to underfunction of the gonadal hormone-producing glands. The fact that senile osteoporosis is more common in women than in men may be related to the fact that gonadal function in old persons is more markedly reduced in females than in males. It is necessary at this point to differentiate between postmenopausal osteoporosis and senile osteoporosis in women. The differentiation is purely an arbitrary one based on age. Those women who develop clinical osteoporosis after menopause at any time up to the age of 65 are said to have "postmenopausal osteoporosis"; those who first develop clinical osteoporosis after the age of 65 are said to have "senile osteoporosis." It is recognized, however, that the estrogen deficiency of the postmenopausal state undoubtedly is one of the contributing factors in the occurrence of senile osteoporosis in these older women. One is on less certain ground when he considers the males. A number of men in the 70 age group have clinical osteoporosis. It has not been possible thus far to demonstrate convincingly that these individuals have a marked reduction in their gonadal function. However, long-standing, untreated eunuchoid males who have been 10 or more years past the normal chronologic age for puberty have an osteoporosis which is clinically indistinguishable from that observed in the senile men. This observation suggests that androgen deficiency may be important as well in the elderly males with senile osteoporosis.

**Osteoporosis of Cushing's Syndrome.** A detailed discussion of Cushing's syndrome and its relation to osteoporosis is beyond the scope of this presentation. Cushing's syndrome is discussed in another section (see Chapter 57). It

is sufficient to indicate that Cushing's syndrome is considered to be the result of an overproduction of certain adrenal cortical steroids which have been called, for the sake of simplicity, the "S" or "sugar" hormone. This hormone causes atrophy of the thymus and lymphoid tissue; has a marked effect upon carbohydrate, protein, and fat metabolisms; and antagonizes the action of insulin. Its metabolic effect could be summarized by the statement that it facilitates the conversion of protein into sugar (gluconeogenesis).

This hormone also has another important property. It interferes with the anabolism of protoplasm; in other words, it is anti-anabolic. Thus it interferes with the building up of protein matrix and the formation of bone; this leads to osteoporosis. The osteoporosis of Cushing's syndrome is one of the most severe forms of osteoporosis encountered. The very fact that the bone disease of Cushing's syndrome is osteoporosis constitutes one of the best pieces of evidence that these adrenal cortical steroids of the "sugar" hormone type are antianabolic rather than catabolic. If these hormones were catabolic, one would expect to find osteitis fibrosa generalisata (increased bone destruction) rather than osteoporosis (decreased bone formation). Other pieces of evidence which favor the interpretation that the "sugar" hormone is antianabolic can be summarized briefly: (1) Patients with Cushing's syndrome (who have an excess of this hormone) show an inability to attain a positive nitrogen balance instead of a propensity to go into a negative balance. (2) When the minimal nitrogen excretion is determined in patients with Cushing's syndrome by administering a high-caloric, high-fat, high-carbohydrate, and very low-protein diet, the nitrogen excretion falls to normal, and is not maintained at a high level as it should be if a catabolic hormone were being produced in excess. (3) It is very difficult with a high nitrogen intake to produce a positive nitrogen balance in patients with Cushing's syndrome. (4) Growth in an epiphyseal cartilage obviously cannot be wiped out by catabolism, but the "sugar" hormone of the adrenal cortex inhibits growth in animals, which would be an impossibility for a catabolic hormone. (5) Experiments in which the "sugar" hormone has been given in combination with pure growth hormone have demonstrated clearly that the "S" hormone inhibits the effect of the growth hormone in animals.

It should be mentioned that the adrenal cortex also produces another type of hormone which is anabolic in its action, and which is spoken of as the "N" or "nitrogen" hormone. This hormone is believed to be very similar in action to the androgen, testosterone. Testosterone compounds will neutralize the effect of the "sugar" hormone. It is not surprising, therefore, that testosterone compounds have a beneficial effect on many patients with Cushing's syndrome and induce in them a retention of nitrogen, phosphorus, potassium, and sulfur in the proportions that exist in protoplasm, and of calcium and additional phosphorus in the proportions that exist in bone. Testosterone compounds are very effective therapy for patients with osteoporosis due to Cushing's syndrome. Estrogenic compounds also have some beneficial effect upon the osteoporosis of Cushing's syndrome, but it is less marked than that of testosterone compounds.

**Osteoporosis Associated with Adaptation Syndrome.** The concepts involved in a consideration of the osteoporosis resulting from the adaptation syndrome of Selye are too complicated for detailed discussion in this section. They can be summarized briefly as follows: When an individual is subjected to any kind of noxious stimulus such as a fracture, an operation, an infection, exposure to heat or cold, or a toxic reaction to a drug, he reacts to the stimulus by setting in motion an adaptation syndrome. One of the integral parts of this adaptation is a change in the production of adrenal cortical hormones which results for a temporary period in an increased production of the "S" or "sugar" hormone. Thus, during this initial or catabolic phase, the adaptation syndrome resembles, from the hormone imbalance point of view, Cushing's syndrome. A few patients have been observed in whom this catabolic phase has persisted much longer than one normally would have expected it to, and in whom, as a result, there has been interference with the anabolism of all tissues, and, in particular, with bone formation. In certain individuals bone formation seems to be particularly inhibited. These patients develop all of the manifestations of osteoporosis. It is recognized, of course, that in almost all of these instances, there has been some degree of immobilization and decreased food intake following the damaging event, and these factors in themselves may be partially responsible for the osteoporosis. However, in metabolic

studies in which these two factors were controlled, a negative calcium balance still occurred following a damaging event.

**Osteoporosis of Acromegaly.** Most patients with acromegaly show a hypercalcuria; a decrease in the density of bone; and serum calcium, phosphorus, and alkaline phosphatase values in the normal range. The bone disease, therefore, is consistent with osteoporosis, and inconsistent with almost any other metabolic bone disease. This decrease in the density of bone occurs in spite of the fact that certain portions of the skeleton of acromegalic patients are growing. The cause of the demineralization of bone is obscure, although five possibilities may be considered: (1) It has been attributed to an accompanying hyperparathyroidism, but there is little evidence for this mechanism because the values for calcium, phosphorus, and alkaline phosphatase in the serum are normal. (2) It has been attributed to an increased stimulation of the adrenal cortex by the pituitary adrenocorticotrophic hormone with the production of hormones which would lead to an osteoporosis similar to that observed in Cushing's syndrome. There is not much evidence to support this possibility. (3) It has been attributed to an excess production of thyrotrophic hormone from the eosinophilic tumor with a secondary hyperthyroidism as a cause for the osteoporosis. This explanation, however, is not supported by convincing evidence. (4) It has been suggested that other parts of the body in acromegaly are growing at the expense of the bone because there is

not enough nitrogen to go around. (5) The bone disorder has been related to decrease in gonadal function which occurs in most cases of acromegaly. It thus becomes similar to the osteoporosis encountered in the postmenopausal state. Although this explanation runs into difficulty in an occasional case in a male who has no apparent gonadal deficiency, it seems to be the most likely hypothesis. Furthermore, patients with osteoporosis due to acromegaly show calcium retention with estrogens, as do women with postmenopausal osteoporosis.

**Idiopathic Osteoporosis.** When all the other types of osteoporosis have been eliminated, there are still a few individuals in whom the cause of the osteoporosis cannot be determined. These include young women with normal ovarian function, as well as young adult males. Many types of therapy have been tried on these cases without benefit, including vitamins A, C, and D; estrogenic hormone; sodium fluoride; and a high protein intake. The only time any of these individuals went into a positive calcium balance with therapy was when serum albumin was given intravenously. This suggests the possibility that serum albumin is a precursor of bone matrix, an observation that needs to be studied further.

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# 67

## Osteogenesis Imperfecta

Edward C. Reifenstein, Jr.

Osteogenesis imperfecta (*fragilitas ossium*; *osteopsathyrosis*) is a hereditary disease which is somewhat similar to osteoporosis. The difficulty seems to be that the osteoblasts do not form a normal amount of extracellular substance, and,

hence, produce too little bone matrix. The end result, it will be seen, will be the same as in osteoporosis. Actually, the osteoblasts are moderately increased in numbers, and hence there is moderate increase in the serum alkaline phos-

phatase in most cases. There are other differences in the bone as well, since the bones are not only thin, but also brittle. In this disease one meets disturbances in other tissues of mesenchymal origin. The scleras almost invariably appear blue because they are very thin and the choroid vessels show through. The blood vessels, fascia, periosteum, and subcutaneous tissues are all very pliable. The bone lesions vary in severity: in some individuals they are incompatible with life, while in others they cause only moderate disability; they tend to improve when adult life is attained. At that time otosclerosis is apt to develop, with nerve deafness. Fractures of the bones occur after less than normal trauma; many patients have had several dozen broken bones during childhood. The fractures seem to heal normally. On x-ray, the bones of the skeleton are thin, but

not decalcified, and the lamina dura is intact. The serum calcium and phosphorus levels are normal, while the serum alkaline phosphatase may be slightly elevated. There is no hypercalcemia or hyperphosphaturia (see Chapter 66, table 77). The condition is apparently a dominant characteristic, and is inherited from one generation to the next. Studies by Dr. Marian Ropes at the Massachusetts General Hospital indicate that positive calcium balance can be attained with both estrogens and androgens in patients suffering with this disorder, and, further, that these individuals are benefited clinically by this type of therapy.

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# 68

## Osteomalacia and Rickets

Edward C. Reifenstein, Jr.

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### GENERAL CONSIDERATIONS

**Definition.** Osteomalacia is that category of "too-little-calcified-bone" in which the decrease in calcified bone tissue is due to inadequate bone formation because of insufficient saturation of the body fluids with calcium and phosphorus.

Hence, osteomalacia is primarily a disorder of calcium metabolism in contrast to osteoporosis which is primarily a disorder of tissue metabolism. As has been pointed out previously, if the ion product of the calcium  $\times$  phosphorus is reduced below normal because there is too little calcium for the level of inorganic phosphorus, or else too little inorganic phosphorus for the level of calcium, precipitation of the calcium phosphate salt into the bone matrix will not occur. In osteomalacia one finds the serum calcium level normal or low, and the serum phosphorus level low or normal; in any case, the product of the serum calcium and the serum phosphorus in milligrams is lower than normal. (The normal serum calcium level is about 10 mg. per cent; the normal serum inorganic phosphorus level is about 3.2 mg. per cent; the normal ion product of the calcium  $\times$  phosphorus is thus about 32. The normal serum alkaline phosphatase level is about 4 Bodansky units.)

Because of the lack of calcification in osteo-

malacia, the bones become weak and more responsive to stress and strain; this leads to increased activity of the osteoblasts, with a high serum alkaline phosphatase level and deposition of wide osteoid seams, which are uncalcified. When osteomalacia occurs in infants and young children, it is called "rickets"; the pathologic physiology is the same, but there are some additional defects in the growing epiphyseal cartilage, particularly faulty calcification of the zone of provisional calcification. The craniotabes, pot belly, Harrison's groove, rachitic rosary, and bowlegs are well-known defects due to rickets and will not be discussed further here. Osteomalacia sometimes is called "adult rickets."

Table 78

## CLASSIFICATION OF CLINICAL TYPES OF OSTEOMALACIA

## TYPES BASED ON COMPENSATORY PARATHYROID OVER-ACTIVITY

Type	Serum Calcium Level	Serum Phosphorus Level	Parathyroid Compensation
1	L	N	None
2	L	L	Partial
3	N	L	Complete

## TYPES BASED ON SEVERITY

Type	Name	Phos-phatase*	Pseudo-fractures	Acalcification
1	Chemical-osteomalacia-with-normal-phosphatase	N	None	None
2	Chemical-osteomalacia-with-high-phosphatase	H	None	Not apparent
3	Milkman's syndrome	H	Present	Not apparent
4	Advanced osteomalacia	H	Present	Present

\* Serum alkaline phosphatase level.

H = high; L = low; N = normal.

**Clinical Types.** Osteomalacia may be classified in several ways. It may be classified in terms of the degree of compensatory parathyroid gland overactivity (see table 78). Three types of cases occur in this classification: (1) those cases in

which parathyroid compensation is completely lacking, where the serum calcium level is low, and the serum phosphorus level is normal; (2) those cases in which there has been partial parathyroid compensation, where the serum calcium level is low, and the serum phosphorus level is also low; and (3) those cases in which there has been complete compensatory parathyroid overactivity, where the serum calcium level is normal, and the serum phosphorus level is low.

Osteomalacia also can be divided into types based upon the severity of the disease process (see table 78). According to such a classification there are four types: (1) "Chemical-osteomalacia-with-normal-phosphatase," in which the serum alkaline phosphatase level is normal, there are no pseudofractures, and there is no evidence of acalcification of bone; (2) "Chemical-osteomalacia-with-high-phosphatase," in which the serum alkaline phosphatase level is high, there are no pseudofractures, and acalcification of bone is not apparent; (3) "Milkman's syndrome," in which the serum alkaline phosphatase level is high, pseudofractures are present, but acalcification of bone is still not apparent; and (4) "Advanced osteomalacia," in which the serum alkaline phosphatase level is high, pseudofractures are present, and acalcification of bone is readily detected.

Milkman's syndrome is an x-ray diagnosis which should be retained to call attention to the fact that one can have underlying osteomalacia when the only x-ray evidence is the ribbon-like zones of decalcification. These zones of decalcification, or pseudofractures, first described by Milkman, tend to occur in symmetric locations. Presumably they are caused by stress at the weak points in the skeleton. The mechanism is probably: (1) partial fracture, (2) filling of the defect with matrix through the activity of the osteoblasts, and (3) failure of the matrix to calcify because of the underlying osteomalacia. The pseudofractures tend to occur in the neck of the femurs, the rami of the pubic and ischial bones, the ribs, and so forth. The underlying osteomalacia in these cases is frequently so mild that it escapes detection, since the bone outside of the area appears normal by x-ray. However, if one determines the blood chemistry, one finds that the serum alkaline phosphatase level is elevated, and this indicates that systemic bone disease is present. Since at least 30 per cent of

the density of the bone must be lost before recognizable changes can be detected in the x-ray films, it is not surprising that a number of early cases are observed in which osteomalacia is present, but in which the degree of general bone involvement is not sufficient to give detectable changes in the roentgenograms.

### CONDITIONS ASSOCIATED WITH OSTEOMALACIA

Osteomalacia can also be classified in terms of etiologic factors (see table 79). The primary cause of osteomalacia is undersaturation of the blood in calcium  $\times$  phosphorus. This may arise in three ways: (1) there may be insufficient absorption of calcium into the system; (2) there may be excessive loss of calcium from the system; or (3) there may be excessive utilization within the system so that the body fluids become depleted. This classification may be expanded to include all of the etiologic conditions at present recognized. These are indicated in table 79.

Table 79

#### CLASSIFICATION OF CAUSES OF OSTEOMALACIA

- I. Insufficient Absorption:
  - A. Low calcium absorption:
    - 1. Low-calcium diet
    - 2. Gastrointestinal disease
  - B. Low vitamin D absorption:
    - 1. Low-vitamin D diet
    - 2. Gastrointestinal disease
    - 3. Vitamin D-resistant rickets
- II. Excessive Excretion:
  - A. Loss from kidney:
    - 1. Calcium as a base in acidosis:
      - a. Pyelonephritis with distal tubular damage
      - b. Fanconi syndrome with proximal tubular damage
    - 2. Low renal threshold:
      - a. Idiopathic hypercalcemia?
      - b. Renal infection?
  - B. Loss from breast:
    - 1. Prolonged lactation
  - C. Loss from placenta:
    - 1. Frequent pregnancy
- III. Excessive Utilization:
  - A. Bone formation too great:
    - 1. Healing osteitis fibrosa generalisata

**Calcium Lack.** Insufficient absorption may result from two major causes: either because there is insufficient calcium absorbed, or else because there is insufficient vitamin D absorbed. Insufficient calcium may be absorbed because the diet is actually low in calcium, or because there is

disease in the gastrointestinal tract which results in inability to absorb calcium. Because of the widespread use of milk as a food, the diet is generally adequate in calcium, and a low calcium intake is rarely a cause of osteomalacia in the United States. However, this appears to be the common cause of osteomalacia in China. Vitamin D lack also is a contributing factor in China.

**Vitamin D Lack and Resistance.** Osteomalacia due to "simple" vitamin D lack is also rare in the United States. The use of a liberal, adequate diet; of foods fortified with vitamin D; and of exposure to sunlight by the large majority of the population probably accounts for the failure to find many causes of osteomalacia due to this type of deficiency. Insufficient absorption of calcium also occurs in rare cases because of resistance to the action of vitamin D. Since these patients do respond to 3 to 10 times the normal amount of vitamin D, it is safe to presume that the defect is a resistance of the body to the primary action of vitamin D.

**Gastrointestinal Disease.** The chief causes of steatorrhea in the United States are: (1) an idiopathic steatorrhea which goes under the diagnosis of nontropical sprue, or, in children, under the diagnosis of celiac disease, and (2) chronic pancreatitis. In these conditions a large amount of fat is retained within the gastrointestinal tract, and the calcium combines with it to form an insoluble soap so that the calcium is not absorbed. Furthermore, vitamin D, which is fat-soluble, also is not absorbed, nor are the other fat-soluble vitamins. Thus, patients who exhibit osteomalacia because of gastrointestinal disease may also show hypovitaminoses A, K, and E. A similar mechanism is responsible for osteomalacia and fat-soluble vitamin deficiencies in patients who have had considerable portions of the gastrointestinal tract removed so that insufficient absorption takes place. Gastrointestinal disease as the cause of osteomalacia and fat-soluble vitamin deficiencies is frequently overlooked; similarly, osteomalacia and fat-soluble vitamin deficiencies as complications of gastrointestinal disease frequently are not recognized. All patients who have undergone gastrectomy should be studied from this point of view.

**Renal Acidosis (Tubular-Insufficiency-Without-Glomerular-Insufficiency).** Calcium can be lost from the body in excessive amounts from three portals: the kidney, the breast, and the

placenta. The latter two are easily recognized and need no further discussion. Calcium can be lost from the body fluids through the kidney in several ways (see figure 126): (1) Calcium can be used as a fixed base to combine with acids either in case of pyelonephritis with distal tubular damage in which the usual mechanisms for making ammonia and excreting acid are impaired, or in the rare condition called the "Fanconi syndrome," in which excessive amounts of acids are produced and all of the possible means of getting rid of them have to be called upon. (2) Calcium can be lost because the renal threshold for calcium has been lowered. Attention should be called to the fact that, in those cases in which osteomalacia occurs because calcium has been used as a fixed base for excreting acids in the urine, the body may also be deficient in other

bases, particularly potassium or sodium. The loss of potassium may result in a low serum potassium level and a high urinary potassium excretion; symptoms may appear similar to familial periodic paralysis, with pain in the extremities and inability to move the arms and legs; there may be a characteristic lowering of the T waves in the electrocardiogram. In those cases in which the sodium is used as a base, the symptoms may resemble adrenal cortical insufficiency, or Addison's disease. Occasionally, one encounters cases in which more than one base is lost at the same time. Some patients are seen who came into the hospital at one time with an osteomalacia, at another time with a syndrome resembling familial periodic paralysis, and at a third time with a syndrome resembling adrenal cortical insufficiency.

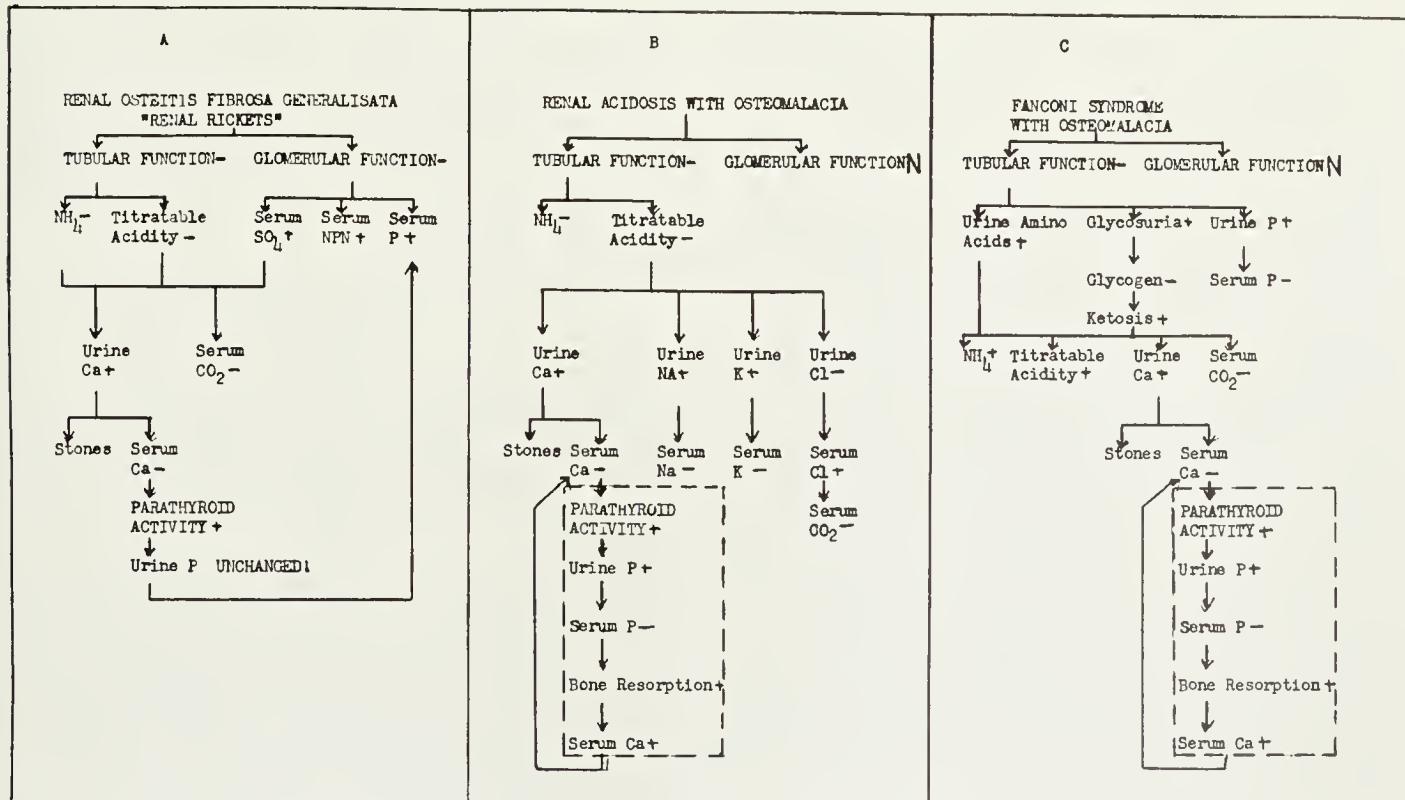


FIG. 126. Diagrams to illustrate the differences in the sequence of events in three types of secondary hyperparathyroidism. (A) Renal osteitis fibrosa generalisata ("renal rickets"). (B) Renal acidosis with osteomalacia. (C) Fanconi syndrome with osteomalacia. Note that the glomerular function as well as the tubular function is decreased in A and as a result the serum phosphorus is high, whereas only the tubular function is decreased in B and C and as a result the serum phosphorus is low. Note that there is acidosis (low carbon dioxide) in all three types, but that in A and B the renal mechanisms for combating it are functioning below normal (low ammonia and low titratable acidity), while in C the renal mechanisms for combating it are functioning above normal (high ammonia and high titratable acidity). Note that even in C the renal mechanism is inadequate to control the acidosis, and hence in this condition (as in A and B) fixed base, particularly calcium, is excreted in excess in the urine. Note that renal calculi occur in all three syndromes. Note that the bone disease in A is osteitis fibrosa generalisata which results from the persistence of the acidosis; and that the serum chemistry (low calcium and high phosphorus) precludes osteomalacia; while in B and C the bone disease is predominantly osteomalacia (low calcium and low phosphorus) but also involves some osteitis fibrosa generalisata which results from the increased bone resorption. Note that in B and C the low serum calcium level can be partially compensated by parathyroid activity, while in A it cannot. Note that in B sodium and potassium may also be lost in the urine in sufficient quantity to produce hyponatremia and hypokalemia. (+) Increased; (-) decreased; (N) normal.

**Fanconi Syndrome.** Certain rare cases present a condition called the Fanconi syndrome, with renal disease involving particularly the function of the proximal tubules so that amino acids are not reabsorbed. As a result, all mechanisms for excreting acids are called upon to function excessively, and the urine contains increased amounts of organic acids, ammonia, and calcium. The loss of calcium results in osteomalacia with typical clinical findings. The renal disease also leads to decreased reabsorption of glucose, which results in hypoglycemia and ketonemia. It may be responsible also for hyperphosphaturia, although this could also be explained by a secondary hyperparathyroidism with the osteomalacia (see figure 126). These cases respond to the same therapy as does osteomalacia due to the other type of renal acidosis (see Chapter 86).

**Idiopathic Hypercalcuria.** Calcium usually disappears from the urine when the serum calcium level falls below 7 mg. %. Cases are found, however, where the kidneys tend to excrete an increased amount of calcium for any given level of calcium in the serum. These patients do not have acidosis, and are classified, therefore, under the heading "Idiopathic hypercalcuria." There is some evidence, also, that the renal threshold for calcium can be lowered by infection of the urine with bacteria, particularly with staphylococcus.

**Osteomalacia Following Removal of Parathyroid Tumor in Osteitis Fibrosa Generalisata.** Finally, the body fluids may be undersaturated because there is excessive utilization of calcium and phosphorus within the body. If a patient has osteitis fibrosa generalisata (increased bone resorption) as a result of having a parathyroid tumor, there will be a compensatory increase in bone formation. If the cause of the increased bone resorption is removed suddenly by surgical removal of the parathyroid tumor, the increased bone resorption will cease immediately. However, the increased bone formation will continue for some time; the calcium and phosphorus in the body fluids will rapidly be sucked into the bone; and, since no more is made available by bone resorption, the serum calcium and phosphorus levels will fall and calcium and phosphorus will practically disappear from the urine. The serum alkaline phosphatase level, which is already elevated, will rise still higher. A most extreme and intractable tetany occurs in this form of osteomalacia. Osteomalacia of this type complicates the

postoperative management of those patients who have primary hyperparathyroidism with bone disease.

**Secondary Hyperparathyroidism.** Almost all cases of osteomalacia are accompanied by secondary hyperparathyroidism. The sequence of events appears to be this: (1) The calcium level in the blood is reduced either because of insufficient absorption, excessive excretion, or excessive utilization of calcium; (2) the low serum calcium level leads to parathyroid hyperplasia; (3) this results in hyperphosphaturia, hypophosphatemia, increased bone resorption, and finally an increase in the serum calcium to offset the low level. Thus a small degree of osteitis fibrosa generalisata may also be present in patients who have osteomalacia. The normal or slightly low serum calcium level and the low serum phosphorus level still leave the body fluids unsaturated, and, as a result, calcium phosphate salts cannot be deposited in the matrix. The uncalcified new bone tissue will be less resistant to stress and strain; this will lead to an increased stimulation of the osteoblasts and to a high serum alkaline phosphatase level.

### OSTEOMALACIA IN THE UNITED STATES

**Etiology.** The various etiologic factors already have been discussed. The main causes in the United States are steatorrhea and renal acidosis from tubular insufficiency without glomerular insufficiency.

**Pathology.** Bone sections from osteomalacia show a decrease in the calcified mass with very few osteoclasts and large numbers of osteoblasts. Most of the trabeculae are covered with osteoid seams which are considerably wider than normal. The marrow spaces are enlarged, but the amount of fibrous tissue is not increased.

**Clinical Manifestations.** Clinically, patients with osteomalacia exhibit anorexia, loss of weight, pain in the bones, deformity of the bones, muscular weakness, renal calculi, chronic pyelonephritis, and urinary tract infections. The number of symptoms is related to the severity of the bone disease. The bone pain is of an aching nature, and the bones are tender to pressure. Because of the frequent involvement of the long bones and the tendency of the bones to bend, a waddling gait is common. Tetany occurs particularly in those cases in which the causative

Table 80  
CHEMICAL FINDINGS IN VARIOUS TYPES OF OSTEOMALACIA

Condition	Serum				Urine				Serum Carotenoids	Vit. A & K Tests	
	Alkaline Phosphatase	Ca	P	CO <sub>2</sub>	Cl	Ca	NH <sub>4</sub>	Tit. Ac.	Sug. Acet.		
"Simple" vitamin D lack.....	H	N or L	L	N	N	L	N	N	0	N	N
Resistance to vitamin D.....	H	N or L	L	N	N	L	N	N	0	N	N
Steatorrhea.....	H	N or L	L	N	N	L	N	N	0	L	L
Renal acidosis (tubular-insufficiency-without-glomerular-insufficiency)	H	N or L	L	L	H	H	L	L	0	N	N
Renal acidosis (Fanconi syndrome) ..	H	N or L	L	L	N	H	H	H	+	N	N
Idiopathic hypercalcemia.....	H	N or L	L	N	N	H	N	N	0	N	N
Osteitis fibrosa generalisata after removal of parathyroid tumor	H	L	L	N	N	L	N	N	0	N	N

H = high; L = low; N = normal; 0 = absent; + = present.

factor is insufficient absorption of calcium, and much less commonly in those due to excessive calcium excretion, since the latter usually are accompanied by an acidosis which tends to offset the tetany.

Three signs are of use in detecting latent tetany: (1) Chvostek's sign, which is elicited by tapping over the facial nerve in front of the ear. A positive result consists of a twitch in the facial muscles, notably those of the lip. Normal adults occasionally show a positive response to this test. (2) Troussseau's sign, which is elicited by reducing the circulation to the arm with a blood pressure cuff for at least three minutes. If the test is positive, the hand assumes the position seen in carpopedial spasm—namely, flexion at the wrist with the fingers flexed at the metacarpophalangeal joints and extended in the interphalangeal joints. (3) Erb's sign, which consists of a response of the motor nerves to less than 6 milliamperes of galvanic current with a cathodal opening contraction. A short period of hyperventilation increases the ease with which these responses can be elicited.

**Laboratory Findings.** The laboratory findings in the different types of osteomalacia have already been mentioned in part. They are summarized in table 80. Attention previously has been called to the fact that in the group labeled "Renal acidosis (tubular-insufficiency-without-glomerular-insufficiency)" one may also encounter a low serum sodium or low serum potassium level. In the Fanconi syndrome, the

blood level of amino acids is not elevated, but the renal threshold for amino acids is lowered. As a result, excessive amounts of amino acids appear in the urine, and there is a high ratio of amino acid nitrogen to total nitrogen in the urine. Glycosuria also occurs in this syndrome.

The amount of calcium in the urine of patients with osteomalacia will depend upon the etiologic factor. In those cases in which the cause is insufficient absorption of calcium, there will be practically no calcium in the urine. However, in those cases in which there is excessive excretion through the kidney, there will be a large amount of calcium in the urine. In those cases in which there is excessive utilization, there will be very little calcium in the urine.

When steatorrhea is the cause of osteomalacia, one often finds the serum carotenoid and vitamin A levels low, and the prothrombin time increased. A fecal fat value of over 10 per cent of the intake, or over 25 per cent of the dried fecal weight, is strongly suggestive of steatorrhea. The serum carotenoid level in a patient treated with all the fat-soluble vitamins serves as an index as to whether or not there is an improvement in the underlying process; thus, the blood vitamin A level will rise with vitamin A therapy, while the carotenoid level will rise only if there is an improvement in the underlying gastrointestinal disorder. Chronic pancreatitis differs from non-tropical sprue in several respects: the duodenal contents are markedly deficient in pancreatic ferment; a larger percentage of the fat in the stools is

in the form of neutral fats as opposed to fatty acids and soaps; meat fibers are often present in the stool, and the fecal nitrogen excretions are increased; the glucose tolerance is normal rather than increased; and normal gastric acidity rather than hypoacidity is the rule.

The x-ray findings in osteomalacia depend to some extent upon the degree of severity of the disease. Osteomalacia commonly involves the extremities and the pelvis, and less frequently the spine and skull. Spontaneous ununited fractures, or pseudofractures, which are typical of Milkman's syndrome, have been mentioned already. The bones are soft and more prone to deformity by bending than they are to fracture. In more advanced cases, the demineralization is readily apparent. The lamina dura will be absent in the long-standing cases. X-ray may reveal renal calculi, or, more commonly, nephrocalcinosis, multiple deposits of calcium in the collecting tubules.

**Diagnosis.** To make the diagnosis of osteomalacia, one relies chiefly on the serum calcium and phosphorus values. The severity of the disease is determined by studying the serum alkaline phosphatase level, and the x-rays for evidences of pseudofractures and generalized demineralization. In establishing the etiologic factor, one considers the history of calcium and vitamin D intake, the presence of gastrointestinal disease or acidosis and renal disease, the amount of calcium in the urine, and the history of frequent pregnancy and prolonged lactation. The special diag-

nostic signs should be employed to uncover latent tetany.

**Differential Diagnosis.** The differentiation of osteomalacia from other metabolic bone diseases depends largely upon the chemical findings (see Chapter 66, table 77). Tetany does occur, of course, in other conditions than osteomalacia (see table 81). It is found in hypoparathyroidism. The differential diagnostic point, in essence, is the fact that the serum inorganic phosphorus level is high in hypoparathyroidism, whereas it is practically always normal or low in patients with osteomalacia. Tetany also occurs as a result of alkalosis. The commonest cause of this is hyperventilation in individuals who are emotionally unstable. Tetany due to this cause is readily recognized by the fact that the serum calcium and the serum inorganic phosphorus levels are normal. Furthermore, there is calcium in the urine in this type, whereas, in the tetany due to hypoparathyroidism and in many of the cases due to osteomalacia, the urinary calcium is practically absent. In the tetany due to alkalosis, the serum total base value will be found to be absolutely or relatively increased, with appropriate changes in the serum carbon dioxide-combining power and in the serum chloride values.

The pathologic physiology of three renal conditions which give rise to metabolic bone diseases are shown in figure 126. Note that "Renal rickets" is really renal osteitis fibrosa generalisata with increased bone resorption due to

Table 81  
CHEMICAL FINDINGS IN VARIOUS TYPES OF TETANY

Type of Tetany	Serum Alkaline Phosphatase	Urinary Calcium	Serum Carbon Dioxide-Combining Power	Serum Chloride
A. Low Calcium:				
1. Low Phosphorus:				
Osteomalacia with decreased calcium absorption.....	H	0	N	N
Osteomalacia with increased calcium excretion.....	H	H	N	N
Osteitis fibrosa generalisata after operation.....	H	0	N	N
2. High Phosphorus:				
Hypoparathyroidism.....	N	0	N	N
B. Normal Calcium and Phosphorus (Alkalosis):				
1. Hyperventilation.....	N	N	L	N or H
2. Vomiting.....	N	N or H	H	L
3. Excess Alkali.....	N	N	H	N

H = high; L = low; N = normal; 0 = absent.

persistent acidosis (see below). All three conditions are accompanied by hypercalcuria and a blood acidosis. The "renal rickets" is recognized readily by the elevated serum phosphorus level, in contrast to the other two conditions which have normal or low serum phosphorus levels. The Fanconi syndrome can be differentiated by the increase of titratable acidity and of ammonia in the urine, in contrast to the decrease of these two "base-sparers" in the urine of patients with osteomalacia due to other types of renal acidosis.

**Treatment.** The treatment of osteomalacia depends again upon the etiology. In those cases in which insufficient absorption is the major factor the primary objective is to give calcium and vitamin D. One to three glasses of milk a day will supply a high intake of calcium, and this can be supplemented by giving 5 Gm. of calcium gluconate, or calcium lactate, dissolved in water, three times a day. Since acidosis tends to alleviate tetany, it is helpful in some instances to make the patient slightly acidotic. Calcium chloride administered by mouth produces a slight acidosis because more chloride is absorbed than calcium. A favorite prescription in the past has been 10 ml. of a 30 per cent solution of calcium chloride diluted in water three times daily after meals. In addition, calciferol (vitamin D<sub>2</sub>) is administered in a dosage of 25,000 to 100,000 units a day. Patients with osteomalacia due to resistance to vitamin D may require as much as 600,000 units of vitamin D daily. Once the osteomalacia is cured, continuation of the vitamin D therapy in large doses not only is unnecessary, but also may lead to hypervitaminosis. The danger point can be determined by following the serum alkaline phosphatase level; when it drops to normal, the vitamin D intake should be reduced to an amount just sufficient to maintain a normal serum calcium level.

The cases of osteomalacia due to insufficient absorption because of gastrointestinal disease require additional medication. Crude liver extract or folie acid should be administered for cases of nontropical sprue. A low-fat diet should be prescribed, and the fat-soluble vitamins should be given in large amounts between meals so they escape being dissolved in what little fat is present. It is important to give *all* of the fat-soluble vitamins, including vitamins A, K, and E.

In those forms of osteomalacia due to excessive

excretion of calcium through the kidney, there are two important principles of therapy: (1) to control the acidosis, and (2) to replace the calcium. Inasmuch as the initial disturbance is a shortage of base, the first item of treatment is the administration of base. This is best given in the form of a salt of a mineral base with an organic acid—for example, sodium citrate, sodium lactate, or calcium gluconate. If low serum potassium or low serum sodium levels are factors, a combination of sodium citrate and potassium citrate should be given. The organic acid is burned after absorption, leaving the base free to help in the excretion of acid in the urine. An organic acid, such as citric acid, which will be largely burned after absorption, can be given in addition to increase the gastrointestinal acidity and hence favor calcium absorption. A favorite prescription consists of 140 Gm. of citric acid and 98 Gm. of sodium citrate dissolved in 1 liter of water; the patient takes 50 to 100 ml. of this mixture, depending upon the amount needed to overcome the acidosis. The second step in the therapy is the administration of agents which will increase the calcium absorption in the gastrointestinal tract—namely, calcium salts and vitamin D. These are used in the same amounts indicated for the osteomalacia due to insufficient absorption. The vitamin D will cause the calcium to be absorbed; the alkali therapy will decrease its loss in the urine. If vitamin D is given alone, a large part of the calcium which is absorbed will be excreted in the urine. If alkali therapy is given alone, very little calcium will be absorbed, so that, in spite of little loss in the urine, the balance will still be only slightly positive. As a matter of fact, if one gives a very high calcium intake and massive doses of vitamin D, so much calcium will be absorbed that, in spite of the large loss in the urine, the patient will be in a positive calcium balance, and the osteomalacia eventually will be cured. Again, the dose of vitamin D should be reduced as soon as there is evidence (a fall to normal of the serum alkaline phosphatase level) that the osteomalacia has been cured.

Cases of osteomalacia due to excessive excretion by way of the breast or placenta are treated in the same way as are the osteomalacias due to insufficient absorption of calcium. Supplementary calcium intake should be given during pregnancy and lactation as a preventive measure.

The osteomalacia resulting from excessive utilization of calcium and phosphorus in compensatory bone formation following the removal of a parathyroid tumor requires prolonged and continuous treatment in order to offset the tetany. The main problem is to keep the calcium in the blood from going into the bones. For this reason, such a patient should be put on a low phosphorus intake. This keeps the calcium in the blood since, without phosphorus, calcium phosphate cannot be precipitated in bone. Milk is high in phosphorus and hence is contraindicated. The only successful way to deal with this situation is to give a continuous intravenous infusion containing calcium gluconate or calcium lactate. For example, 100 ml. of 10 per cent of calcium gluconate in 1000 ml. of 5 per cent glucose can be administered intravenously by slow drip daily. Agents such as A.T. 10 or vitamin D are of very little benefit in raising the serum calcium level in this form of osteomalacia. Both of these agents increase calcium absorption from the gastrointestinal tract, but this is not the difficulty. As has been pointed out, the main problem is that the calcium is taken up into the bone too rapidly. In a matter of weeks to months the "hungry bones" become filled up

with calcium and less subject to stresses and strains, the serum alkaline phosphatase level falls to normal, and the hypocalcemia and tetany disappear. Originally, it was the practice to reduce the risk of developing this form of tetany following parathyroid operation by performing only a partial resection of the parathyroid adenoma when there was a marked degree of bone disease present. This procedure is less imperative now that the mechanisms by which the tetany arises are more clearly understood.

**Results of Treatment.** The response to treatment of patients with osteomalacia is most spectacular. In a relatively short time the pseudofractures disappear, the bones become much stronger, normal growth occurs where epiphyses have not yet united, and there actually may be a decrease in the amount of nephrolithiasis and nephrocalcinosis. This is due to the fact that the acidosis has now been overcome with alkali, and the patients cease to form more stones while they continue to pass some of those already present, so that the total number often decreases.

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## 69

### Osteitis Fibrosa Generalisata

Edward C. Reifenstein, Jr.

Definition  
 Primary Hyperparathyroidism  
   Without Osteitis Fibrosa Generalisata  
   With Osteitis Fibrosa Generalisata  
 Secondary Hyperparathyroidism

#### DEFINITION

Osteitis fibrosa generalisata is that category of "too-little-calcified-bone" in which the defect is increased resorption of bone. There are two main causes: excessive amount of parathyroid hormone, and acidosis. The increased bone resorption leads to decreased bone strength, and this,

in turn, to an increased activity on the part of osteoblasts, and hence to a high serum alkaline phosphatase level. However, the compensatory bone repair never catches up with the bone destruction. The turnover of bone is thus tremendous, and increases the longer the condition exists, providing the calcium and phosphorus intake remains constant. Hyperparathyroidism is primary when the excess hormone is independent of the need, and secondary when the excess hormone is in response to a need.

## PRIMARY HYPERPARATHYROIDISM

**Without Osteitis Fibrosa Generalisata.** An excess of parathyroid hormone causes an increase of phosphorus in the urine, a decrease of phosphorus in the serum, and an undersaturation of the calcium × phosphorus product in the body fluids. If the intake of calcium and phosphorus through the gastrointestinal tract is sufficient, this undersaturation is met, and there is no need for increase in bone resorption. Thus many cases of primary hyperparathyroidism are not accompanied by any bone disease. Because of a generally high intake of calcium and phosphorus in the form of milk in the United States, increasing numbers of cases of hyperparathyroidism are being recognized in which there is no bone disease. When the Massachusetts General Hospital series stood at 64 cases, there were 35 with bone disease, and 29 without (see table 82). Support for

Table 82

ANALYSIS OF CLINICAL TYPES OF PRIMARY HYPERPARATHYROIDISM FROM MASSACHUSETTS GENERAL HOSPITAL SERIES

	With Bone Disease	Without Bone Disease	Total
With kidney disease.....	24	28	52
Without kidney disease.....	11	1	12
Total.....	35	29	64

the contention that cases can exist without bone disease comes from studies in which the bones of patients who subsequently proved at operation to have parathyroid tumors were biopsied at a time when the disease was active without revealing any evidence of osteitis fibrosa generalisata under the microscope. Furthermore, if patients with primary hyperparathyroidism with bone disease are administered either a large amount of calcium or a large amount of phosphorus, the bone disease can be cured while the parathyroid tumor is still present. These procedures are not to be recommended as therapy, however, because the excess of minerals aggravates the renal condition. As a matter of fact, renal involvement is the most important feature of primary hyperparathyroidism. When the Massachusetts General Hospital series stood at 64, there were 52 cases

with kidney disease, and only 12 without kidney disease (see table 82).

~~The diagnosis of "primary hyperparathyroidism" can be made from the serum calcium and serum inorganic phosphorus levels.~~ Once the diagnosis has been established, one can then go on to determine whether the patient has "primary-hyperparathyroidism-with-bone-disease" or "primary-hyperparathyroidism-without-bone-disease." This can be decided from the level of the serum alkaline phosphatase, which will be normal in those cases without bone disease, and elevated in those cases with bone disease.

**With Osteitis Fibrosa Generalisata.** The clinical manifestations of primary hyperparathyroidism may be due to the hypocalcemia per se, to the renal disease, or to the bone disease. The first two of these conditions are discussed elsewhere (see Chapter 56), and will not be presented here. Patients who have primary hyperparathyroidism with bone disease complain of bone pain, which at first may be indefinite and attributed to rheumatism, arthritis, or neuritis. As the disease progresses, the pains increase in severity and are aggravated by sneezing, coughing, etc. The bones become very tender to pressure. All degrees of skeletal decalcification are met, from the minimal to the extreme case where the patient has lost practically all of his skeleton. As the decalcification increases, the bones tend to become deformed, and the long bones to bend. There may occur deformities of the pelvis similar to those seen in osteomalacia and osteoporosis—namely, eel-fish vertebra, crushed vertebra, herniation of the nucleus pulposus into the end-plate of the vertebra, wedging of the vertebra, etc. There may be decrease in stature, pigeon-breast deformity, or disappearance of the neck into the thorax. However, the bones in osteitis fibrosa generalisata are more brittle than those in osteomalacia, so that fracture rather than bending is the rule. At the same time that the skeleton is becoming generally decalcified, there is no decalcification of the teeth. However, the jaw may become so soft that the teeth will fall out. The skull is frequently involved, in contrast to osteoporosis and osteomalacia.

In addition to the generalized decalcification, there are localized lesions consisting of bone cysts and bone tumors. The cysts are fibrous

tissue-lined cavities filled with fluid. The bone tumors are solid masses of osteoblasts and osteoclasts with the supporting cells of the bone marrow; they have been called osteoclastomas, or could as well be spoken of as osteoblastomas; they resemble benign giant-cell tumors. The tumors tend to occur in certain areas of predilection, notably in the jaws (epulis), the metacarpals, the metatarsals, and the ends of the long bones. While every case of epulis is not due to hyperparathyroidism, this diagnosis must be considered in each case.

On roentgenographic examination one finds generalized decalcification. This can be recognized in the early cases by absence of the lamina dura about the teeth (fig. 127). The skull with generalized decalcification shows a "ground-glass" or a "moth-eaten" appearance (fig. 128). However, the thickness of the skull has nothing to do with the decalcification. By x-rays, the bone cysts and the bone tumors look alike, and it is impossible to tell one from the other. It is only by following the course of these lesions after the parathyroid tumor has been removed that one can determine which was which; the bone tumor will be replaced with solid bone, while the cyst will remain as a cyst. X-ray films of the chest sometimes will show the tumor in the mediastinum, and occasionally deviation of the esophagus can be demonstrated with a swallow of barium. In addition, the x-ray films may show nephrocalcinosis or nephrolithiasis.

The other features of primary hyperparathyroidism are discussed in detail in another section

(see Chapter 56). Some of the points in differential diagnosis are shown in Chapter 66, table 77, p. 657. The treatment is surgical removal of the pathologic parathyroid tissue; x-ray irradiation of the parathyroid glands has been of little avail. After surgery, the blood chemistry returns to normal in a few days if the patient has no bone disease, and no special management is required. However, if bone disease is present, then intractable tetany may result. This has been discussed in Chapter 68, p. 672. Bone destruction stops abruptly, but compensatory bone repair continues, and calcium and phosphorus are sucked into the bones. The compensatory increase in the process of bone repair tends to persist for quite a long time after the parathyroid tumor has been removed, and the end result is overdense bone.

### SECONDARY HYPERPARATHYROIDISM

As has already been pointed out in Chapter 68, p. 665, almost all cases of osteomalacia have a secondary enlargement of the parathyroid glands with an excess of parathyroid hormone being produced. Thus, all of these cases will show, in addition to osteomalacia, a moderate degree of osteitis fibrosa generalisata.

There is another form of secondary hyperparathyroidism which is called renal osteitis fibrosa generalisata or "renal rickets." The latter term is a misnomer because the bone disease is not rickets (osteomalacia), but osteitis fibrosa generalisata. The primary difficulty is tubular and glomerular disease which results in persistent

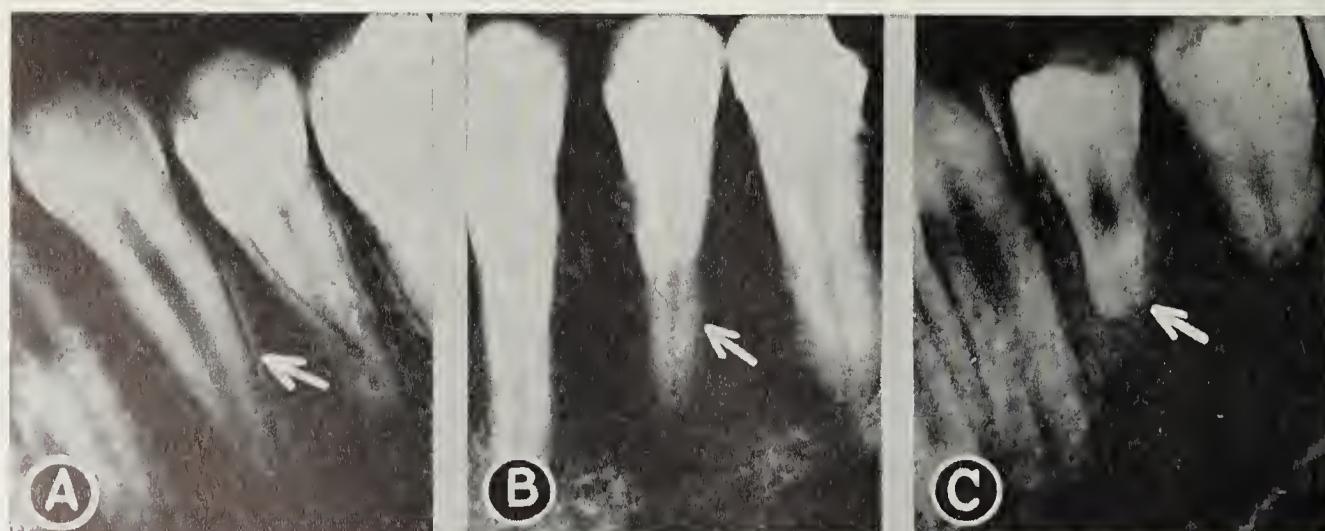


FIG. 127. Photographs of x-ray films of teeth comparing those of the normal individual with those of patients with hyperparathyroidism and hypoparathyroidism. (A) The teeth of a normal individual. Note the presence of the lamina dura (arrow). (B) The teeth of a patient with hyperparathyroidism. Note the absence of the lamina dura (arrow). (C) The teeth of a patient with hypoparathyroidism. Note the blunted ends of the teeth (arrow).

acidosis. One finds renal insufficiency which is long-standing and severe; an elevation of the serum inorganic phosphorus and nonprotein nitrogen levels; a normal or slightly low serum calcium level; a severe acidosis with a low car-

since studies have shown that parathyroid hormone is not effective in lowering phosphorus levels that are elevated for this reason, it is clear that the bone disease in this particular condition does not arise from excess parathyroid hormone, unless one postulates that the parathyroid hormone acts directly on bone. The fact that the bone disease in renal osteitis fibrosa generalisata can be overcome by measures which overcome acidosis, but not the phosphate retention, favors the interpretation that the acidosis is responsible for the increased bone resorption.

In these cases, the acidosis affects calcium metabolism in two ways: (1) It produces an excessive excretion of calcium in the urine as a fixed base combined with the acids, which tends to lower the serum calcium level; and (2) it increases bone resorption, which tends to raise the serum calcium level. The net result, however, is usually that the serum calcium level is somewhat low so that the saturation of calcium  $\times$  phosphorus would be less than normal were it not for the fact that there is phosphorus retention. In some cases, in spite of the phosphorus retention, the saturation is below normal, and some evidence of osteomalacia can be found on biopsy of bone, where a moderate increase in the width of the osteoid seams can be seen.

The phosphorus retention may also influence the bone by the following effects: (1) decreased phosphorus excretion in the urine, (2) increased serum phosphorus level, (3) increased fecal phosphorus excretion, (4) formation of insoluble calcium phosphate in the gut, (5) decreased calcium absorption from the gut, and (6) increased bone resorption because of undersaturation of calcium and phosphorus. The low serum calcium level would also serve as a stimulus to the parathyroids to increase their hormone production. However, it has been shown that the parathyroid hormone does not influence the phosphorus level when phosphorus retention is due to renal disease.

A comparison of the pathologic physiology of renal osteitis fibrosa generalisata with that of two other renal conditions which give rise to metabolic bone diseases is shown in figure 126. This has already been discussed in Chapter 68, p. 667, in connection with the differential diagnosis of osteomalacia. A comparison of some of the chemical findings in renal osteitis fibrosa generalisata with those of certain other bone diseases is given in Chapter 66, table 77, p. 657.

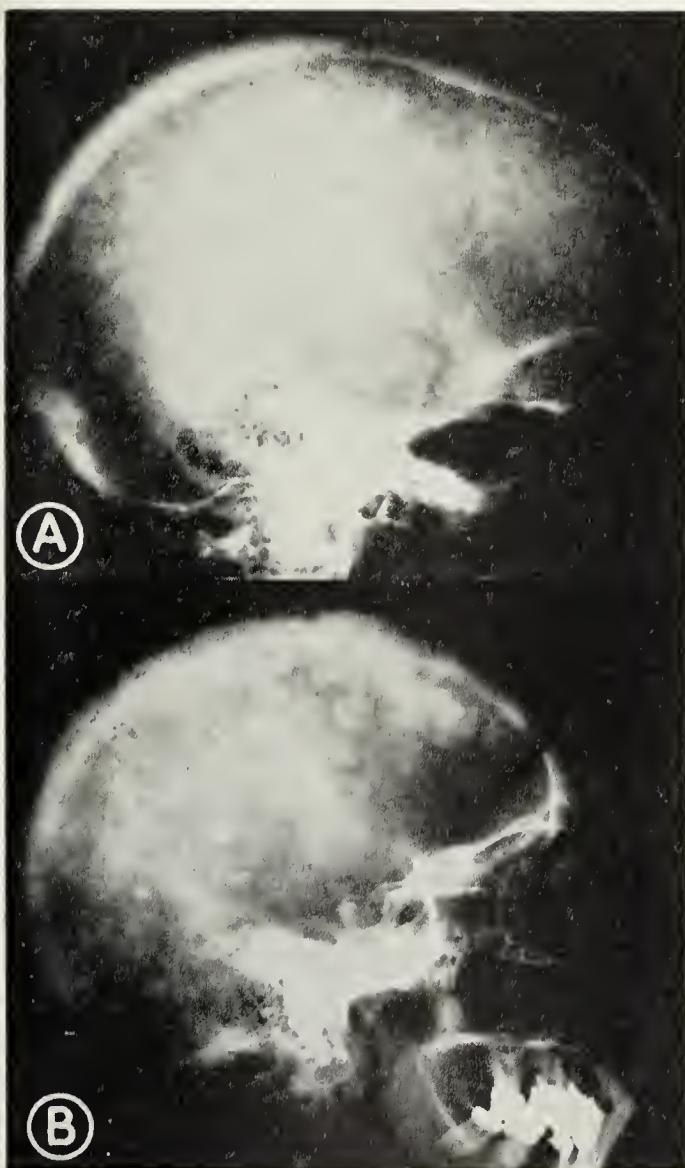


FIG. 128. Photographs of x-ray films of skulls comparing osteitis fibrosa generalisata with Paget's disease of bone. (A) The thick "moth-eaten" skull of a patient with osteitis fibrosa generalisata. (B) The overgrown skull of a patient with Paget's disease. Note the area of destruction in the frontal region.

bon dioxide-combining power, and either a high serum chloride or a low serum sodium; a high serum alkaline phosphatase level; arteriosclerosis of the Mönckeberg type; and calcium deposits around the joints. Clinically, and by biopsy, the bone disease is osteitis fibrosa generalisata and is identical with that found in primary hyperparathyroidism. Since the serum phosphorus is elevated as a result of the renal disease, and

The main therapeutic indication is the administration of some alkaline salt (for example, sodium citrate) in sufficient quantity to restore the carbon dioxide content of the serum to a normal level. Administration by mouth of 2 to 3 Gm. of sodium citrate four times daily is usually sufficient. Citric acid can be added to the sodium citrate to make the intestinal contents more acid and to increase the absorption of calcium. It is recognized that the overcoming of the acidosis by this therapy in the presence of a low serum calcium level may lead to tetany. However, in actual experience, this turns out to be more theo-

retic than real. Overcoming the acidosis stops the loss, but does not produce a satisfactory retention, of calcium. A high calcium intake can be assured by administering, together with the alkali, vitamin D in large quantities, and a calcium salt. The usual amounts given are 50,000 units of calciferol (vitamin D<sub>2</sub>) daily by mouth, and calcium gluconate, 5 Gm. three times daily by mouth.

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## 70 Osteopetrosis

Edward C. Reifenstein, Jr.

Osteopetrosis (marble bones, Albers-Schönberg disease) is a hereditary disease in which the primary defect is decreased bone resorption. As a consequence, one observes marked density of all bones. There is decreased remodeling of bones, and primary trabeculae fail to be resorbed and replaced by criss-cross secondary trabeculae. This results in a peculiar "celery" appearance of the metaphyseal bone. In some incidences the fetal bones can be seen within the long bones. In spite of the increased density, the bones are brittle and fractures are common. Because of the lack of bone resorption, the bone marrow be-

comes crowded and cannot function properly, so that the patients develop a myelophthisic anemia and then compensatory enlargement of the liver and spleen. Other symptoms arise from the crowding of nervous tissue by bone—for example, pressure on the cranial nerves, with optic atrophy, nystagmus, hydrocephalus, and so forth. No therapy is known to be effective.

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## Hypoparathyroidism

Edward C. Reifenstein, Jr.

In patients who develop hypoparathyroidism as a result of the surgical removal of the parathyroid glands, or who suffer from idiopathic hypoparathyroidism, there is insufficient resorption of bone. Since bone formation continues unabated in these cases, in the long run the bones become too dense. In the parathyroidless individual, the serum calcium level falls because of phosphorus rise, and not vice versa. This means a tendency to supersaturation, which in turn could explain the tendency in hypoparathyroidism for calcium to be deposited in abnormal locations. In some cases, however, the serum calcium level falls to such a point that there is insufficient saturation of calcium  $\times$  phosphorus for deposition of calcium phosphate salt in matrix, and the patient actually has a mild degree of osteoma-

lacia. This probably accounts for the acalcification of teeth which sometimes is seen in hypoparathyroidism. Furthermore, if a child develops this disease at about 10 years of age, the roots of the molar teeth which have not yet formed at that age will not develop. Therefore, hypoplasia of the teeth with blunted roots (see figure 127) is a useful finding to establish the diagnosis of hypoparathyroidism, and to indicate the date of onset of the disease. The other manifestations of hypoparathyroidism are discussed elsewhere in Chapter 56 (see also Chapter 66, table 77, p. 657).

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In Chapters 72-75 brief mention will be made of some nonmetabolic bone diseases which are occasionally mistaken for metabolic bone diseases.

## Polyostotic Fibrous Dysplasia

Edward C. Reifenstein, Jr.

Polyostotic fibrous dysplasia (osteitis fibrosa disseminata; Albright's syndrome) is a localized bone disease which frequently is mistaken for hyperparathyroidism with bone disease. Polyostotic fibrous dysplasia is a curious disease which shows a disseminated osteitis fibrosa of both the hyperostotic and the hypoostotic type, with a segmental distribution which suggests a neurologic or embryologic relationship; areas of

brown cutaneous pigmentation with a distribution suggesting some connection between them and the bone lesions; and sexual and somatic precocity in females, but not in males. The condition can be differentiated from hyperparathyroidism because the bone lesions are not generalized. Furthermore, the bone lesions are hyperostotic as well as hypoostotic, which is most unusual in hyperparathyroidism. The skull

abnormalities are spotty in distribution and consist of multiple localized lesions with normal bone elsewhere. The lesions will involve the multiple bones of one extremity or one digit, and entirely miss the other extremity or other digit. The occiput, the metatarsals and metacarpals, the phalanges, the upper ends of the femurs, and the tibias are the sites of predilection. The epiphyses of the phalanges, metatarsals, and metacarpals usually, but not always, escape involvement. The base of the skull is especially prone to be very dense and hyperostotic; this may lead to proptosis of one or both eyes. There may be a marked prominence in the region of the occiput. Pathologic fractures are common, but usually heal well. The upper ends of the femur, when involved, usually show outward bowing which produces the "shepherd-crook deformity" (fig. 129).

On histologic examination, the involved bone shows the characteristic findings of osteitis fibrosa, except that occasionally there are islands of cartilage. The bone age is usually precocious in those females who develop precocious puberty. The brown cutaneous pigmentation exhibits very irregular outline in contrast to the relatively regular outline observed in neurofibromatosis. The mucous membranes of the mouth sometimes may be involved. The pigment is melanin. The sexual precocity in females is a true precocity, since the pituitary and ovarian glands function in a normal manner. A case has been observed in which catamenia was established before the age of one, the woman bore several normal children, and finally developed menopause at the age of 54 after 53 years of normal ovarian function! The patients grow rapidly and are large for their chronologic ages; however, because of early closure of the epiphyses, they usually are rather short at maturity. No consistent abnormality in gonadal function has been found in male patients. It is believed that the precocity results from the premature release of the follicle-stimulating hormone of the anterior pituitary gland as a result of some hypothalamic disturbance, which would result in the production of estrogen in the female, but not of androgen in the male. The blood chemistry is normal in

Polyostotic fibrous dysplasia, although there may be some elevation of the serum alkaline phosphatase (see Chapter 66, table 77, p. 657). The bone lesions show only a slight tendency to progress, never clear up spontaneously, and are not radio-



FIG. 129. Photographs of x-ray films of the pelvis comparing metastatic malignancy with polyostotic fibrous dysplasia. (A) The pelvis of a patient with metastases of a hypernephroma (arrow) of the ileum. (B) The pelvis of a patient with polyostotic fibrous dysplasia, showing "shepherd-crook" deformity (arrow) of the femur.

sensitive. Hyperthyroidism has been observed in a number of the cases. The only known treatment is orthopedic therapy for the skeletal deformities and fractures.

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## Paget's Disease

Edward C. Reifenstein, Jr.

Paget's disease of bone (osteitis deformans) is a localized bone disease in which the primary lesion is bone destruction. The etiology of the primary lesion is not known. The parathyroid glands have been studied and found to be normal in cases with Paget's disease. The question has been raised as to whether a vascular disorder is responsible, because the condition intensifies with age, is frequently associated with arteriosclerosis, tends to run in families, and exhibits evidences of too much circulation of blood in the area of the lesions. For example, ~~X~~ the skin over the bone lesions is warm, a fact which is an aid in the diagnosis of the location of the lesion. The condition that develops in the lesion is analogous to an arteriovenous shunt, like an aneurysm, and as a result of this there may be an increase in the total blood flow up to 20 times the normal amount. Several cases of cardiac failure have been reported arising from this cause. Paget's disease of bone is also related to the ~~X~~ stress and strain placed on the skeleton. The bones most frequently involved are those that are subjected to the greatest stress. For example, the "sacrum" is involved more often than the "lumbar vertebrae", the lumbar more often than the "thoracic", the thoracic more often than the cervical vertebrae, and the "lower extremities" more often than the upper. The skull is frequently involved also, and apparently the pull of the temporal muscles has some influence on this site of the lesions.

Paget's disease of bone is a fairly common disease. It is said to be present in 3 per cent of all persons over 40 years of age. Pathologically the lesions resemble, to some extent, those of osteitis fibrosa generalisata, in that they both have marked "vascularity", marked "fibrosis", about half of the surfaces with "osteoclasts and bone resorption", half with "osteoblasts and bone repair", and normal calcification, since the osteoid seams are normal in width. However, osteoblastomas and brown tumors are rare in Paget's disease. ~~X~~ The arrangement of trabeculae is good in osteitis fibrosa generalisata, so that mechanical advan-

tage is still maintained, whereas it is very poor in Paget's disease, so that the bone has a very poor architectural value. Finally, the mosaic structure and cement lines in the bone are rare and regular in osteitis fibrosa generalisata, and common and irregular in Paget's disease. This is presumably due to the fact that ~~X~~ bone destruction and bone repair occur over and over again in the same area, resulting in a bizarre and patternless mosaic of cement lines (see figure 128).

If one accepts that ~~X~~ initial lesion is due to bone destruction, one can explain all of the other findings in Paget's disease very easily. The destruction, which leads to hypercalcuria and renal calculi, also causes weakened bones that have a tendency to fracture, and that respond in a greater manner than normal to stress and strain. As a result of this, there is an ~~X~~ increase in osteoblastic activity that leads to an elevation of the serum alkaline phosphatase level, an increase in bone repair, and an overgrowth of bone which is compensatory and which results in deformity. However, the bone destruction continues, and areas that have just been repaired are destroyed again.

Evidence that the initial lesion is bone destruction is obtained from three sources. (1) The histology of the advancing edge shows definite bone destruction. (2) In certain situations, particularly in the skulls of women after menopause, one can find "normal bone", then "bone destruction", and then "bone repair" as three adjacent zones which are visible by x-ray. Furthermore, these zones progress with time in the same relationship to each other. (3) The progression of the lesions thus gives further evidence that the initial lesion is bone destruction.

~~X~~ The laboratory findings of Paget's disease (see Chapter 66, table 77, p. 657) include a normal serum calcium level, a normal or slightly high serum inorganic phosphorus level, a high serum alkaline phosphatase level, and a high urinary calcium level which sometimes leads to urinary calculi formation. By x-ray one observes in-

creased density of bones with coarse trabeculation, an increased size of the bone, bowing of the extremities with partial infractions, and finally the three zones at the advancing edge of the lesions.

~~X~~Three complications occur in patients with Paget's disease: (1) renal calculi, (2) osteogenic sarcoma, and (3) chemical deaths from metastatic calcification with immobilization. ~~X~~Renal calculi result from the hypercalcuria. ~~X~~Osteogenic

~~X~~sarcoma occurs quite commonly in patients who have had a preexisting Paget's disease. It should be suspected in those patients who experience a marked increase in the intensity of their bone pain or other symptoms, or a sudden marked increase in their serum alkaline phosphatase level. Whenever a patient with Paget's disease is immobilized as a result of a fracture or some other illness, the amount of bone repair is sharply decreased, and osteoporosis of disuse occurs. Since bone destruction continues unabated, a huge amount of calcium which before immobilization has been put back into bone must now be excreted into the urine. The quantity of calcium may exceed the ability of the kidney to excrete it. As a result, hypercalcemia will develop, with nausea, vomiting, dryness of the mouth, and even, chemical death.

The treatment of Paget's disease must be divided into the treatment of ambulatory cases and the treatment of immobilized cases. In ~~XX~~ambulatory patients there are three objectives: (1) to decrease bone resorption, (2) to increase bone repair, and (3) to decrease bone pain. The first of these, the decreasing of bone resorption, can be

brought about by giving: (a) a high calcium and phosphorus intake—for example, two glasses of milk per day; (b) vitamin D to increase calcium absorption, in a dosage of 50,000 units three times a week; and (c) alkalinizing salts—for example, sodium citrate, 2 Gm. three times a day. However, there is a danger of increasing the kidney stones with the alkali medication. In order to increase bone repair, one keeps the patient as active as possible and, if the patient is a postmenopausal woman, administers estrogen. ~~X~~Bone pain at times can be decreased by giving large amounts of ascorbic acid, up to 1000 mg. per day. ~~X~~The treatment of the immobilized patient with Paget's disease is directed toward one objective, to decrease the amount of calcium that must be excreted in the urine. To do this, the patient takes a low calcium and phosphorus intake, avoids milk, omits vitamin D, drinks large amounts of water, and, when there is hypercalcemia, is given dextrose and saline intravenously. Immobilization is reduced to a minimum, and estrogens are given to maintain bone formation at a maximum rate. It should be pointed out that estrogens should not be given to young adult males because there is a danger of permanently damaging the testes and producing sterility.

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### Osteitis Fibrosa Localisata

Edward C. Reifenstein, Jr.

Osteitis fibrosa localisata ("solitary bone cyst") produces solitary cystic bone lesions which, on biopsy, are indistinguishable from those of osteitis fibrosa generalisata. These lesions are found particularly at the ends of long bones, where they not infrequently lead to

pathologic fractures. The fact that the serum calcium, phosphorus, and alkaline phosphatase levels are normal serves to indicate that such cysts are not manifestations of an underlying metabolic bone disease.

## Miscellaneous Disorders of Bone

Edward C. Reifenstein, Jr.

Multiple Myeloma  
Metastatic Malignancy  
Hypervitaminosis D (Vitamin D Poisoning)  
Boeck's Sarcoid  
Other Nonmetabolic Bone Disorders

### MULTIPLE MYELOMA

Although most of the bone lesions of multiple myeloma appear sharply demarcated by x-ray, one can sometimes find bone involvement (Kahler's disease) which is quite difficult to distinguish by x-ray from hyperparathyroidism. Furthermore, the serum calcium level may be high in myeloma, and, when it is, hypercalcuria is also present and there may be nephrolithiasis. The serum phosphorus level is usually normal or high, but a few cases have been shown to have serum phosphorus levels as low as in hyperparathyroidism. The serum alkaline phosphatase level is rarely, if ever, elevated in multiple myeloma, which is an important differential point (see Chapter 66, table 77, p. 657). Furthermore, the presence of an increased amount of circulating protein, particularly globulin; the presence of the Bence-Jones protein in the urine; and the finding of plasma cells in the peripheral blood and in the sternal bone marrow by biopsy, are of considerable aid in the diagnosis of multiple myeloma. Some success in relieving pain in multiple myeloma has been reported recently with stilbamidine.

### METASTATIC MALIGNANCY

The x-ray appearance of the bone lesions in metastatic malignancy usually is differentiated from that of the bone lesions of hyperparathyroidism with bone disease, since the areas involved usually show sharply demarcated lesions, and areas of normal bone are found quite readily. The serum calcium level may be high, and there may be hypercalcuria and kidney stone formation. The serum phosphorus level is usually normal, occasionally elevated, and only very rarely decreased (see Chapter 66, table 77, p. 657). The

serum alkaline phosphatase level may be elevated. A primary focus should be sought in the breast, prostate, kidneys (hypernephroma), bronchus, or thyroid.

### HYPERVITAMINOSIS D (VITAMIN D POISONING)

In patients who have received excessive amounts (150,000 units per day or more) of vitamin D, there may be produced the syndrome of vitamin D poisoning. This includes symptoms such as hypercalcemia with hyperphosphatemia, or in some cases even hypophosphatemia; impaired renal function; hyposthenuria; proteinuria; polyuria and polydipsia; anorexia; lethargy; and constipation. It is not clear whether the disorder results from a hypervitaminosis or from a toxic property of vitamin D. It seems probable that the manifestations are due to an excess of the known actions of vitamin D: (1) to decrease calcium absorption from the gastrointestinal tract, and (2) to increase phosphorus excretion in the urine. The sequence of events may be: (1) increased calcium absorption, (2) increased serum calcium level, (3) decreased parathyroid activity, (4) decreased urinary phosphorus excretion, (5) increased serum phosphorus level, (6) supersaturation of the blood with respect to calcium phosphate, and (7) precipitation of calcium phosphate in abnormal sites (metastatic calcification). These sites include the kidneys, bronchi, alveoli of the lungs, mucous membrane of the stomach, blood vessels, and other tissues. It seems probable that, in those cases of hypervitaminosis D in which there is hypophosphatemia, there has been a very low calcium intake. This would eliminate the sequelae of the first action of vitamin D, including hyperphosphatemia, and would lead to hypophosphatemia. The blood chemistry (see Chapter 66, table 77, p. 657) would then simulate hyperparathyroidism. The diagnosis should be clear from the history of excessive intake of vitamin D (see Chapter 48).

### BOECK'S SARCOID

In Boeck's sarcoid, one may find bone changes, hypercalcemia, hypercalcuria, high serum alkaline phosphatase level, and kidney stones. The absence of hypophosphatemia and the presence of hyperproteinemia and hyperglobulinemia are an aid in establishing the diagnosis of sarcoid (see Chapter 66, table 77, p. 657). Furthermore, the bone lesions of sarcoid are confined mostly to the hands and feet, and there is no generalized demineralization. There is some evidence that the abnormal calcium metabolism is the result not of the bone disease per se, but of a disordered blood chemistry. In this respect, sarcoid resembles hyperparathyroidism.

### OTHER NONMETABOLIC BONE DISORDERS

A large group of conditions which involve bone might be mistaken occasionally for metabolic bone diseases. These include lymphoma, benign metastasizing hemangioma, Gaucher's disease, xanthomatosis, and chronic radium poisoning. Since these conditions are rare, they will not be discussed in this chapter.

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## Section 4—Disorders of Muscle

# 76

## General Considerations

Frank H. Tyler

The neuromuscular unit consists of the anterior horn cell and the muscle fibers which it innervates. Failure of muscle function may be the consequence of disturbance at various levels of this unit. Thus, there may be interference with the normal coördination of impulses coming to the lower motor neuron, as, for example, when the long motor tracts of the spinal cord are damaged; there may be disease of the anterior horn cell itself, such as occurs in acute poliomyelitis; there may be interference with the normal transmission of the impulse from the neuron to the muscle across the neuromyal junction, as is found in myasthenia gravis; or there may be damage to the muscle syncytium itself, as in the muscular dystrophies.

Of the many diseases which profoundly influence muscular function, the majority are the result of processes which injure the central nervous

system or the peripheral nerves. The disorders which are discussed in this section, particularly the muscular dystrophies, are thought by some, including the author, to be fundamentally the result of abnormalities in the metabolism of muscle. In spite of the fact that this is unproved, they are included with the known metabolic disorders of muscle, such as thyrotoxic myopathy, in this part of the text. Similarly, myasthenia gravis is probably a disorder of metabolism at the neuromyal junction. Peroneal muscular atrophy has been included because it is frequently confused with the muscular dystrophies, although it is a disease which primarily affects peripheral nerves and the spinal cord.

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# 77

## Progressive Muscular Dystrophy

Frank H. Tyler

History and Terminology  
Childhood Type  
Clinical Pattern  
Complications  
Laboratory Data  
Pathologic Anatomy  
Pathogenesis  
Inheritance

Treatment  
Facioscapulohumeral Type  
Clinical Pattern  
Inheritance  
Pathogenesis  
Laboratory Data  
Therapy

**History and Terminology.** Progressive muscular dystrophy (*dystrophia musculorum progressiva*; primary myopathy) was described by a number of different authors in the latter half of the nineteenth century. A confusingly great num-

ber of names have been used since that time to designate these diseases. This has created the false impression that a great number of variants exist. Duchenne reported a group of patients with muscular enlargement as well as atrophy,

who have since been referred to as the "pseudo-hypertrophic type." Gowers, in his monograph, described 220 cases of the same type. Leyden and Möbius called attention to a clinically similar group in which, however, muscular enlargement was lacking. Thus arose the name "simple atrophic type." Later Gowers distinguished a form of muscular dystrophy with atrophy of distal instead of proximal muscles. There is reason to doubt that the "distal form" described by Gowers is a form of muscular dystrophy. Such cases are extremely rare and will not be described here.

In this same period, Landouzy and Déjérine described a form of muscular dystrophy in which the facial and pectoral girdle muscles were the first to be involved, which they called the "facioscapulohumeral" type. Erb reported a "juvenile dystrophy" which differed from the facioscapulohumeral type only in that the face showed little or no significant abnormality. In addition, a congenital or infantile form has been described, but the separation of these cases from amyotonia congenita and the Werdnig-Hoffmann syndrome is difficult and unsatisfactory.

Later authors have assumed that all of these groups represent only insignificant variations of a single disease process. Whether this be true or not, a practical clinical purpose is served by classifying muscular dystrophy into only two types. Between these types there are differences in the mode of inheritance, age of onset, rate of progression, and prognosis. Nearly all cases fit well into one or the other of these two types. The first, which will be called the *childhood type*, begins in early childhood, nearly always affects males, is frequently inherited as a sex-linked recessive Mendelian trait, involves axial (trunk) and pelvic musculature initially, is often accompanied by muscular enlargement, is rapidly progressive, and is seldom compatible with survival to adult life. This type includes at least most of the patients previously described under the headings "pseudohypertrophic," "simple atrophic," "Duchenne," and "Leyden and Möbius" types.

The second or *facioscapulohumeral type* appears in late childhood or in adolescence, is characteristically inherited as a Mendelian dominant affecting both sexes in approximately equal numbers, involves facial and pectoral girdle muscles early, is only rarely accompanied by muscular enlargement, and incapacitates only a small

percentage of affected persons before they are old. This group includes Erb's "juvenile dystrophy" and the type of Landouzy and Déjérine.

### CHILDHOOD TYPE

**Clinical Pattern.** Progressive muscular dystrophy of childhood usually appears in boys before they reach the age of six. Some children manifest weakness or enlargement of the calf muscles before they learn to walk. In a few rare individuals, manifestations which are indistinguishable clinically from the childhood disorder develop in adult life. Occasionally a girl is seen whose clinical picture fits this better than that of any other well-defined neuromuscular disorder although, more frequently than not, atypical features are found on close study (see Inheritance, Chapter 25).

Such children are normal at birth, and their early muscular and other development is indistinguishable from that of a normal child. The most frequent initial complaint is that the child falls frequently. On examination, easily demonstrable weakness and atrophy of the peroneal, tibial, thigh, pelvic girdle, spinal, and pectoral girdle muscles are found. These usually have not been recognized by the patient or his family. The onset and progression are usually so insidious that it is nearly impossible to date the events accurately in the history. An occasional individual will relate the onset to an acute illness or injury. So far as can be determined, these have no causal relation but do affect the course of the disease in a fashion which will be pointed out below.

There are rarely any symptoms other than those relating directly to the muscular disability. An occasional child will complain of aching or nagging pain in the legs, or of muscular cramps. The disease is steadily progressive without striking remission or relapse, although the patients may feel better and stronger on certain days. When these patients are confined to bed by acute illnesses or other causes, disproportionately rapid increase in the severity of the disease occurs during the period of inactivity. For this reason, body casts should be avoided.

As the disease becomes more severe, a characteristic pattern of muscular wasting becomes evident which is the best diagnostic criterion of the disease. Slight symmetric weakness of the entire group of facial muscles, usually most marked in

the zygomaticus and orbicularis oris, occurs in some cases. These changes result in only minimal changes in facial expression, a transverse smile, and some pouting of the lips. The other muscles supplied by cranial nerves are essentially normal. The cervical muscles are rather diffusely affected, but all of them remain functional to a certain extent, with the extensors and sternocleidomastoids least seriously impaired. In contrast, certain of the muscles of the pectoral girdle may be entirely absent. Among the earliest to disappear are the middle and lower fibers of the trapezius, the rhomboids, the latissimi, and the sternal head of the pectoralis major. The serratus anterior usually is only moderately involved. This combination of changes results in elevation and slipping out and forward of the scapulas, which stand out like wings behind when tension is placed on them by pushing against a wall or raising the arms (fig. 130). The anterior chest develops a flattened ap-

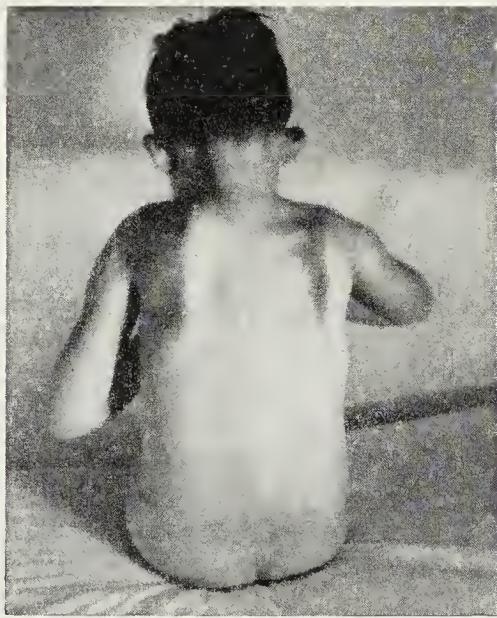


FIG. 130. Loss of lower trapezius and other scapular muscles in moderately advanced childhood dystrophy.

pearance which is sometimes complicated by depression of the sternum (*pectus excavatum*). The deltoid sometimes shows striking atrophy of its upper half in contrast to the relatively intact lower part.

The triceps and biceps brachii are moderately to severely involved. The brachioradialis becomes atrophic and even disappears at an early stage but the other forearm muscles retain fair strength and mass until most of the central musculature is very atrophic. The intrinsic muscula-

ture of the hand is not severely involved until quite late in the disease.

Soon all of the axial musculature becomes involved and the changes progress rapidly. Severe lumbar lordosis and inability to extend the trunk on the pelvis without support are soon evident. This leads to the very characteristic maneuver which these children develop of literally climbing up their own legs with their hands in order to bring the trunk to its precarious vertical position. They fall whenever this carefully maintained balance is disturbed.

All of the thigh muscles are involved, but the process is usually most severe in the quadriceps femoris. The lower leg shows a striking disproportion between the severely involved tibial and peroneal groups and the usually much less weak calf and foot muscles. Sometimes the tibial group shows a significantly more severe degree of atrophy than the peroneal, but in the average patient the involvement is similar in the two groups. The muscular loss is quite symmetric at all stages of its development, a fact which is useful diagnostically.

The gastrocnemius and soleus show a striking and diagnostically useful sign in some of these cases. Indeed, the very first sign, as has been noted already, may be the enlargement of the calf muscles. This process has been referred to as "pseudohypertrophy." It is symmetric when present, and is seen in other muscles as well, most frequently the deltoid and triceps. It occurs in other diseases of muscle infrequently and irregularly. Although the affected muscles are weaker than might be expected from their size, severe loss of strength is unusual. They do not become atrophic or weak at a rate as rapid as in the other involved muscles. The enlarged muscles feel firm and doughy in contrast to normal or atrophic muscles.

Neurologic examination shows only defects which are secondary to the muscular atrophy and loss of tone. The reaction to electric stimulation is normal except that increased potential is required to produce contraction in the involved muscles. Deep tendon reflexes may be depressed or absent, depending on the amount of atrophy and loss of tone in the muscles tested. Sensation is intact in all modalities; coördination is markedly impaired by the muscular weakness, but no evidence of deficiency of cerebral or spinal motor centers is found. Intellectual development is not

hindered by the disease, although mental deficiency may be present as a separate hereditary or developmental anomaly.

When the disease becomes severe (fig. 131), the patients are confined to bed or a wheelchair because of their inability to stand and walk without support. Strength may still be fair in the hands and forearms. The facial involvement is not progressive. Normal facial movement is the rule even in the completely bedridden patient with little evidence of functional voluntary muscle elsewhere.

**Complications.** As the activity of the patient is reduced by his disability, deforming contractures frequently develop. The Achilles tendons and hamstrings are involved most frequently. During this same period, marked scoliosis and kyphosis may develop because of the severity of the atrophy in the axial musculature. These may result in very severe deformities, particularly of the chest, but seldom are they severe enough to produce symptoms of respiratory insufficiency.

Certain of these patients become quite obese when they are bedfast. There is often a high dietary intake, sometimes in relation to the emotional problems of invalidism. Obesity is a serious problem because of the manner in which it complicates nursing care and increases disability. Only by proper supervision of intake and by help with emotional problems can the obesity be controlled. Other patients become quite emaciated and have little muscle or subcutaneous tissue.

An unusual but apparently directly related complication is the development of congestive heart failure as the result of involvement of the myocardium by the dystrophic process. In the majority of patients in whom there are no other

signs or symptoms of cardiac disease, sinus tachycardia is found. Symptoms of cardiac involvement might be much more frequent if the muscular disability did not limit activity so severely early in the disease. The congestive failure is often mild and responds to the usual management. Although it can be fatal, remissions frequently occur in which cardiac signs and symptoms may no longer be detectable clinically, and they may not recur during many ensuing years of life. Electrocardiographic abnormalities are found in many cases.

In general, the patients are normal in other respects, except for the occurrence of unrelated congenital anomalies. Congenital heart disease is the most common associated disorder.

The disease process itself is seldom fatal, but most of the patients die in adolescence or early adult life from infections, most frequently respiratory, which develop as a result of their disability.

**Laboratory Data.** The laboratory findings are not highly specific and not so helpful in diagnosis as the clinical findings. The blood is consistently normal in the absence of complications. The urine is negative. The spinal fluid seldom shows any abnormalities. No really significant abnormality of the blood chemical determinations has been found which is of diagnostic usefulness.

The only diagnostically useful determination is the concentration of creatine and creatinine in the urine. The best available evidence indicates that ingested or endogenous creatine is stored mainly in muscle. Amounts in excess of the quantity that can be stored lead to a marked increase in serum levels of creatine and result in excretion of creatine in the urine. Creatinine is



FIG. 131. (*Left*) Extreme muscle atrophy in advanced childhood muscular dystrophy (without pseudohypertrophy). (*Right*) Intact orbicularis oris in the same patient.

the anhydride of creatine, and when formed it is excreted in the urine. Creatinine appears to be derived by a nonenzymatic change in creatine phosphate which occurs either *in vivo* or *in vitro* at a constant rate. For this reason it is thought that the 24-hour excretion of creatinine is an accurate measure of the total body store of creatine and thus of the functional muscle mass in the body.

Normal adult males excrete little or no creatine in the urine, but females and children may excrete small amounts of creatine even on a creatine-free diet.

The usual laboratory procedure for the determination of creatine and creatinine is to measure the creatinine and then to convert the creatine to creatinine by heating in acid solution, and to redetermine the creatinine. The creatine can then be estimated from the difference multiplied by a factor (1.32) for conversion of creatinine to creatine. It is sometimes helpful to make a ratio from the two values obtained in the laboratory. The ratio of *creatinine to creatine and creatinine expressed as creatinine* nearly always exceeds 0.80 in the normal individual. The creatinine excretion is proportional to the age and weight (muscle mass) of the subject.

The creatinine excretion is frequently expressed as an index which is derived by dividing the 24-hour creatinine excretion in milligrams by the body weight in kilograms. Normal values are usually between 14 and 25, depending on the muscular development of the individual.

More or less in proportion to the reduction in muscle mass, patients with muscular dystrophy of childhood excrete much less than the normal amount of creatinine and greatly increased amounts of creatine in the urine. Even in the early stages, the ratios described above are below 0.50 and may be much lower, even below 0.10. Such ratios are found only very rarely in any other disorder. It must be kept in mind, however, that other neuromuscular and metabolic diseases may lead to creatinuria, and care must be taken not to put undue reliance on the finding in differential diagnosis.

**Pathologic Anatomy.** The atrophic muscles appear white or fatty. Microscopically, the abnormal findings are limited to the muscle with the exception that the numbers of anterior horn cells in the spinal cord are slightly decreased. This is probably the result of the loss of muscular

tissue. In the muscle there is marked infiltration of fat and fibrous tissue which replaces most of the muscle fibers. Early biopsies show swelling of muscle fibers, with diameters of 100 to 200 microns in contrast to a normal diameter of 50 microns. Very small fibers are also seen in increased numbers. The cross striation tends to persist, although some large fibers may appear homogeneous. More than a normal number of sarcolemmal nuclei are seen, and these are sometimes centrally located.

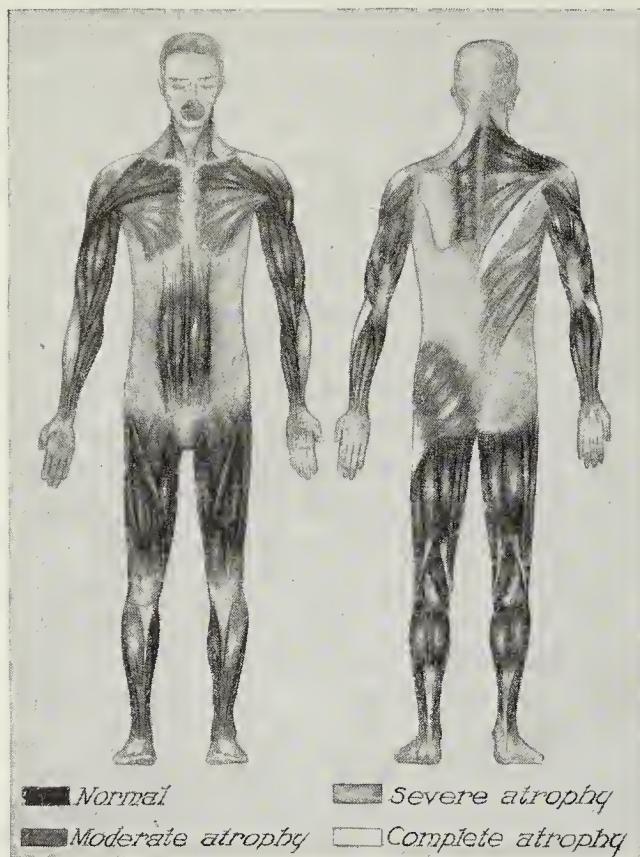
The lesions are similar in all types of dystrophy and do not differ from the changes which are seen in muscular atrophy as the result of lesions of motor neurons. By staining the nerve sheaths, fibers, and endplates, it has been possible to show, however, that branching nerve fibers can be demonstrated in the dystrophies in contrast to the empty nerve sheaths in neural muscular atrophies.

**Pathogenesis.** The pathogenesis of progressive muscular dystrophy is obscure. The amount of creatinuria seems definitely greater than is found in other diseases of muscle with a comparable amount of loss of muscle mass. Indeed, in certain types of atrophy the maintenance of a normal ratio in spite of greatly reduced creatinine is in striking contrast to the findings in these patients.

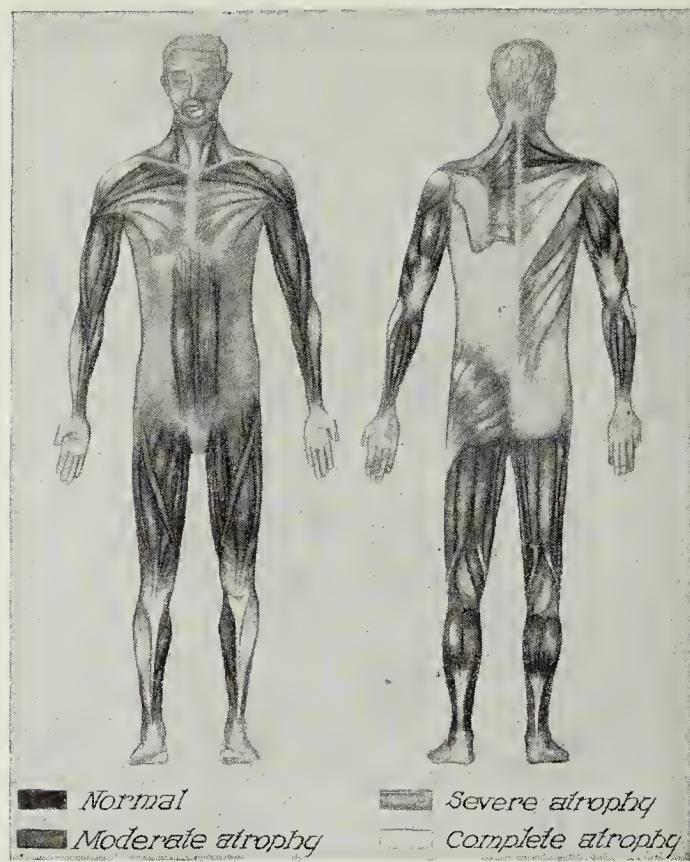
The pattern of development of muscular atrophy is remarkably similar from one patient to another. It bears an accurate relation to the order of development of muscles in the embryo, those muscles which appear earliest manifesting weakness and atrophy before muscles which develop later. Even when one part of a muscle arises earlier than another part, the atrophy follows this order.

Thus the upper fibers of the trapezius arise with the muscles innervated by the cranial nerves at a very late period, while the lower fibers are among the earliest of the girdle muscles to develop. As dystrophy progresses in the patient, the lower fibers of the trapezius become involved, in striking contrast to the preservation of the upper fibers. No other relationship to aging in normal or dystrophic subjects is apparent. It seems possible that the loss or deficiency of some enzyme system could be responsible for this pattern of muscular wasting.

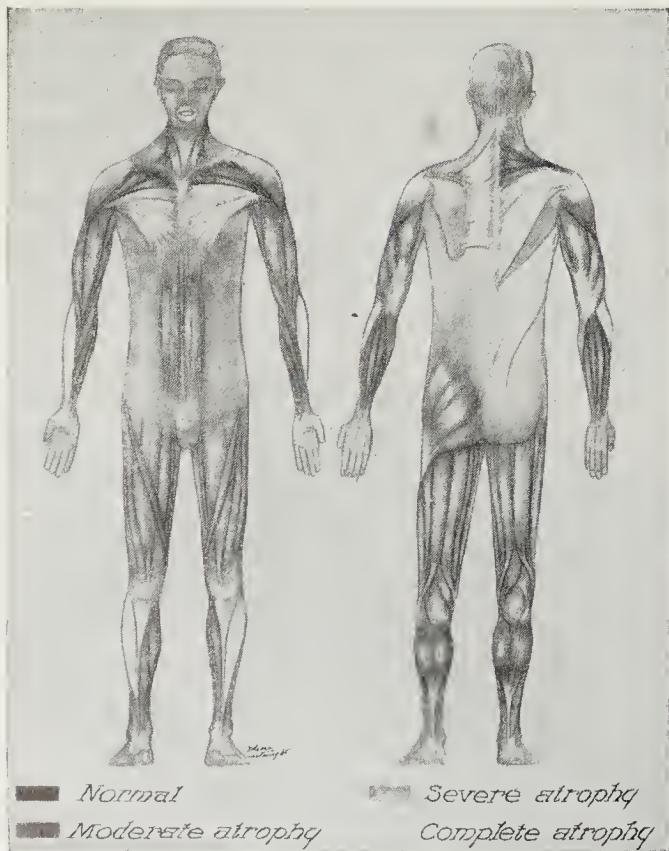
**Inheritance.** This type of muscular dystrophy is frequently familial in character, and more than one male child of a family often manifests the



A



B



C

FIG. 132. Semidiagrammatic representations of the pattern of muscular atrophy in facioscapulohumeral dystrophy at three stages (A, B, C) in the development of the disease. (Courtesy, Tyler and Wintrobe: *Ann. Int. Med.*, 32: 1950.)

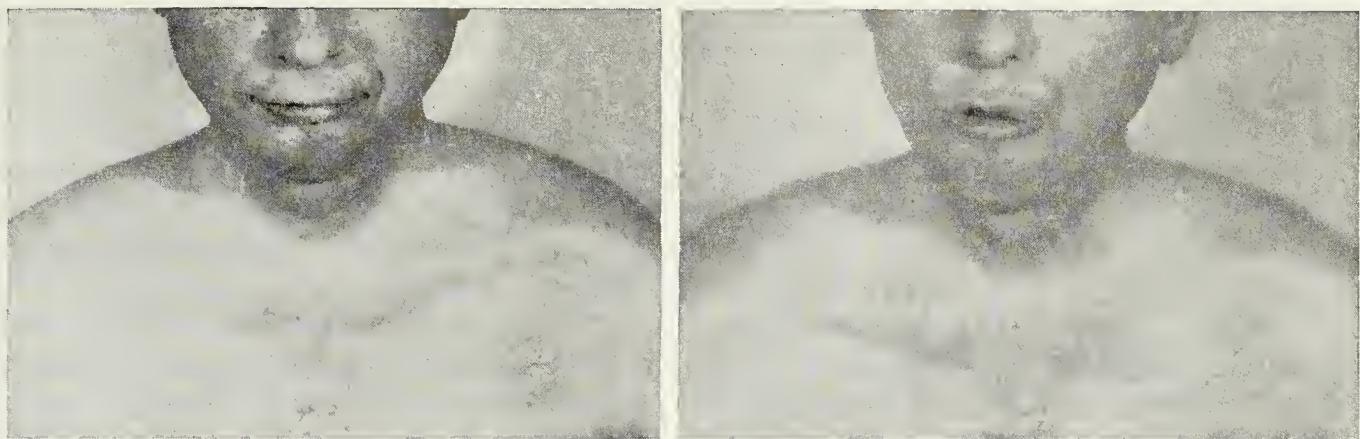


FIG. 133. Facial changes in facioscapulohumeral dystrophy. The illustration on the left shows the face at rest, and the one on the right shows the asymmetry of the orifice produced on attempting to whistle by pursing the lips.

disease. The parents are normal. In some families, male children of various members of the female line are affected. This fact, together with its nearly complete limitation to males and its frequent apparently sporadic occurrence, suggests that the condition depends usually on the transmission of a sex-linked recessive gene.

Families have been reported in which the dominant type of inheritance seemed to be present. It is possible that essentially the same abnormality is transmitted by different genes in different families. The study of the problem is complicated by the probably fortunate fact that the patients only rarely have children and therefore the trait can be traced only in collaterals of involved individuals.

**Treatment.** See under Facioscapulohumeral Type.

#### FACIOSCAPULOHUMERAL TYPE

**Clinical Pattern.** Facioscapulohumeral dystrophy is a disease which is closely related to childhood dystrophy. The average age of onset is 13 years, but ranges between 9 and 20 years. A few patients even beyond 50 years of age are found on close examination to have the disorder, although they have not recognized their disability. As this implies, the degree of involvement may be extremely slight; others are incapacitated before the age of 20.

The pattern of muscular involvement (fig. 132) differs from that of other dystrophics, as is indicated by the name. Facial involvement is nearly always present. All of the facial muscles are involved in the process but the orbicularis oris shows a patchy and asymmetric atrophy which results in asymmetric movements of the mouth and inability to pucker the mouth or whistle

normally (fig. 133). There is weakness of the orbicularis oculi and diffuse flattening of the facial expression. The appearance and particularly the asymmetric movements about the mouth are extremely characteristic. The diagnosis may be suspected after watching the patient's face while he gives his history. Careful observation of the characteristic movements in cases of this type is a great aid in the recognition of minimal involvement in other patients.

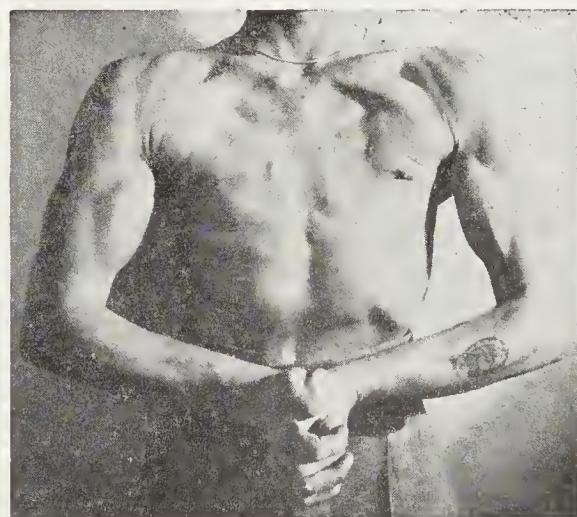


FIG. 134. Ballet dancer and weight lifter with minimal facioscapulohumeral dystrophy. Note the marked atrophy of the sternal head of the pectoralis major and marked work hypertrophy of adjacent, as yet intact, fibers. The relative loss in the brachioradialis is also apparent.

The muscles of the pectoral girdle are involved early in the course of the disease in the same pattern as in childhood dystrophy. Frequently there is complete atrophy of a pair of muscles with no evident disease in a nearby pair of muscles (fig. 134). The patients cannot raise their arms above their heads as a result of the loss of

muscles of the pectoral girdle, but they frequently maintain normal strength in the forearms and hands until an advanced age.

The axial and pelvic musculature is not involved extensively until late in the disease, but atrophy in the tibial and peroneal groups begins early.

These patients show the same complications and associated abnormalities as patients with childhood dystrophy, but there are fewer associated congenital anomalies, and heart disease due to dystrophy, and contractures, are extremely rare. The average patient lives out a normal life span, becoming incapacitated only very late in life if at all.

**Inheritance.** The disease is inherited as a pure Mendelian dominant with complete penetrance. This, plus the fact that involved persons are not incapacitated during the childbearing period, accounts for the many involved persons sometimes found in a single family.

**Pathogenesis.** The pathogenesis is as obscure as that of the other dystrophies.

**Laboratory Data.** Laboratory examinations yield no abnormalities except creatinuria which is usually not so pronounced, and creatinine excretion is not so greatly reduced, as that seen in childhood dystrophy. Typical ratios of creatinine to total creatine and creatinine are about 0.50.

**Therapy.** Treatment of both of these disorders is entirely unsatisfactory at the present time. Vitamin E and inositol and modified vitamin E preparations, pyridoxine, testosterone, and glycine have enjoyed popularity, but there is no

well-documented, long-term evidence of satisfactory results.

Two factors are of definite importance in the management of these diseases. Avoidance of prolonged bed rest and inactivity, and encouragement of the patient to maintain as active and normal a life as possible, are indicated to prevent the rapid progress which is associated with inactivity, as well as for the psychic health of the patient. A diet which is adequate in all normal requirements but which will not result in progressive weight gain is desirable. No evidence is available that any type of dietary supplement beyond the normal level is of value.

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# 78

## Myotonia Dystrophica

Frank H. Tyler

Definition  
Clinical Pattern  
Inheritance  
Treatment

**Definition.** Myotonia dystrophica (myotonia atrophica, myotonic dystrophy, Steinert's disease) is a familial disease characterized by

myotonia, muscular wasting of a characteristic pattern, cataracts, testicular atrophy, and frontal baldness.

**Clinical Pattern.** Except for the myotonia, which frequently develops many years before the other manifestations, the disease usually begins

in middle or late life. Myotonia consists of an inability to relax a muscle normally after its contraction, and is the result of repetitive discharge of the motor end-plate. It is a symptom which may be seen in an occasional patient with any of several other neuromuscular disorders. It is seen most characteristically in the adductors of the thumb. The patient's inability to let go after shaking hands may give the clue to the proper diagnosis. The muscular atrophy which develops is in some respects similar to that in the diseases described above. A different type of facial involvement occurs, however, which leads to a very expressionless facies. The weakness is most marked in the levator of the eyelid, and severe ptosis of the lid is a uniform finding late in the disease. This becomes so severe that the patient must tip his head back to see straight ahead. The "dystrophic" facial movements of facioscapulohumeral dystrophy do not occur. The voice becomes nasal and expressionless, mainly as a result of the loss of strength in the lips. Atrophy of the temporalis is usually severe.

Loss of the sternocleidomastoids is disproportionately marked, but the other muscles of the anterior part of the neck are also frequently so atrophic that the trachea is seen immediately beneath the skin. There is extreme difficulty in flexing the neck, but extension is usually moderately good as the result of preservation of the spinalis group of muscles.

The loss in other muscle groups is very similar to that of childhood dystrophy, except that much earlier and more severe atrophy of the muscles of the leg, forearm, hands, and feet develops which may even exceed in severity that of the central musculature.

These patients, whether male or female, also develop cataracts and progressive alopecia, usually frontal, at an early age. Testicular atrophy with androgenic deficiency usually develops in males. They are frequently sterile and sometimes impotent. Ovarian deficiency occasionally develops in females. This is seldom severe enough to interfere with the menstrual pattern or fertility. Certain patients manifest only one of the symptoms of this complex, but myotonia is usually demonstrable if a careful search is made.

Neurologic examination reveals no sensory or other motor abnormalities.

Two rare but distinct diseases are closely related to myotonia dystrophica and need mention

in order that they may not be confused with it. Myotonia congenita (Thomsen's disease) is a familial disorder of dominant inheritance in which lifelong myotonia, which is most severe following rest, excitement, or anxiety, occurs. None of the other manifestations of myotonia dystrophica occur and the disease is benign, occasioning only slight inconvenience to those manifesting the trait. Paramyotonia congenita is an even more rare disorder in which myotonia occurs only following exposure to cold. It is also familial, of dominant inheritance, of lifelong duration and benign character. It is genetically separate from both of the other myotonias. Both of these disorders respond to quinine as described below.

**Inheritance.** The trait is inherited as a typical Mendelian dominant, but certain members of a given line may manifest only one or two of the usual group of findings. Myotonia is the most common finding on physical examination, while cataracts are often mentioned in family histories.

**Treatment.** Quinine has a mild curare-like action at the motor end-plate, and thus relieves the myotonia. Although symptomatic relief of the myotonia is usually good, the drug has no effect on the progress of the muscle atrophy or other degenerative aspects of the disease. The usual dose is 0.3 to 0.6 Gm. orally, repeated as needed about every six hours. Mild toxic symptoms such as tinnitus may develop before enough quinine has been given to obtain satisfactory relief of the myotonia. Some patients find these symptoms more distressing than the myotonia and prefer not to take quinine except on special occasions when the myotonia is troublesome in a particular activity.

Surgical management of the cataracts when they are mature is indicated.

Administration of androgen and estrogen therapy may give symptomatic benefit, but a relation of these hormones to the pathogenesis of the disease is not established.

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## Peroneal Muscular Atrophy

Frank H. Tyler

Definition  
 Terminology  
 Clinical Pattern  
 Inheritance  
 Treatment

**Definition.** Peroneal muscular atrophy (Charcot-Marie-Tooth disease) is a disease, frequently familial, which begins with atrophy of the peroneal and tibial muscle groups. This is followed by atrophy of the forearm, leg, hand, and foot muscles with associated sensory changes and sometimes loss of function of the lateral or posterior columns of the spinal cord or both.

**Terminology.** Peroneal muscular atrophy is a disorder which is difficult to fit into the pattern of neuromuscular diseases. For many reasons it appears to be the result of primary lesions in the spinal cord and peripheral nerves, in contrast to the dystrophies, in which the primary pathology appears to be in the muscles themselves. However, because the condition presents special problems in differentiation from the dystrophies and is inadequately discussed by some neurologic textbooks, it is discussed here.

**Clinical Pattern.** As the name suggests, the earliest sign in the great majority of cases is weakness and atrophy of the peroneal muscles. The tibial muscles usually are also involved either simultaneously or shortly after the onset of the disease, and foot drop develops. Many patients complain initially that they must drag the toes, and that they have difficulty in going upstairs. They may wear out the toes of their shoes. The onset usually occurs in adolescence, and progress is very slow and insidious. Occasional patients give a history of onset after an acute illness or trauma, but the significance of this is not clear.

The weakness and atrophy involve the muscles of the feet, lower leg, hands, and forearms, but seldom progress to involve any more proximal muscles.

Frequently there are associated sensory losses which may involve temperature and light touch only, or all modalities of sensation. The pattern of loss is variable, most frequently distal in the extremity, but a root type of distribution may occur instead of a peripheral nerve distribution. Sometimes no anatomic pattern can be identified in the distribution which is found.

A certain number of these patients have spinal cord lesions which involve the long tracts, particularly the pyramidal tracts. As a result, spasticity, hyperactive reflexes, and positive Babinski signs may be found. Less frequently the posterior columns are involved, with loss of proprioception and vibratory sense, usually limited to the feet. Such patients may or may not have pyramidal disease as well.

Most of these patients live to be adults and the disease progresses very slowly after that time. A few become bed or wheelchair invalids. Associated anomalies are unusual.

**Inheritance.** Many of the patients give a history indicating that other members of the family are involved. Inheritance is most usually typical of the dominant type. Because of the many minimally affected cases, very careful examination may be necessary before the hereditary pattern becomes evident.

**Treatment.** No specific treatment is of any value. Orthopedic procedures are sometimes beneficial in the management of the foot drop and spasticity. Some of the partially invalidated individuals may be returned to useful occupations by means of physiotherapy and re-education, in combination with the use of suitable supports.

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## Myasthenia Gravis

Frank H. Tyler

Definition
Clinical Pattern
Complications
Pathology
Pathogenesis
Diagnosis
Treatment

**Definition.** This disease is characterized by weakness and easy fatigability which most frequently affect the facial, oculomotor, laryngeal, pharyngeal, and respiratory muscles.

**Clinical Pattern.** Myasthenia gravis occurs at all ages and in both sexes. The disease most frequently appears, however, in the third or fourth decade. There is no significant familial incidence.

The onset may be in facial or, more frequently, oculomotor muscles. The weakness of facial muscles and drooping of the eyelids, which may be unilateral at first, give rise to a placid facial expression which is extremely characteristic and not unlike that of sleep. The facial folds tend to disappear. The smile is frequently more snarling than truly pleasant in appearance, a point of some embarrassment to certain patients. Diplopia is a symptom which frequently appears early but is also a transient and intermittent symptom. Occasionally progression to complete paresis of ocular movement occurs.

The laryngeal and pharyngeal muscles may be the first to manifest abnormalities of which the patient is aware. Choking and aspiration of food are common and obviously serious symptoms. Fluids may flow from the nose when swallowing is attempted as a result of paresis of the palatal muscles.

Fatigability of an unusual type is the most characteristic part of the disorder in these as well as in the general skeletal muscles. Even though initial strength is not greatly impaired, fatigue and weakness appear following repetitive effort after only a few contractions. With complete rest of the involved muscle partial recovery is only a little delayed as compared with a normal muscle, but the fatigue and weakness recur promptly on renewed activity.

The involvement of tongue, laryngeal, and

facial muscles results in abnormal speech of a rather feeble nasal quality which becomes more severe and sometimes not understandable if the patient continues to talk for a short time. This is in striking contrast to the psychoneurotic patient who also complains of weakness but talks interminably.

Skeletal muscles not infrequently are involved diffusely in the process. This rarely occurs in the absence of involvement of muscles innervated by cranial nerves. The proximal muscles of the pectoral girdle and the respiratory muscles are those most commonly involved among the skeletal groups. The story of easy fatigability and relatively prompt partial recovery is usually obtained easily. It is most characteristically demonstrated by having the patient perform a repetitive motion with some involved muscle. Sometimes no abnormality may be demonstrated in one muscle although it is easily evident on ordinary activity at other sites. As the process becomes more severe and of longer duration, it also tends to be more extensive.

The process is aggravated to a variable extent by a number of factors. The most frequent of these are excitement, general fatigue, loss of sleep, menstruation, high-carbohydrate meals, and the intake of alcohol.

Remissions are common and almost always occur after weeks or months of difficulty. They may be partial or complete. Relapses are also completely unpredictable as to time of occurrence or severity, but usually reproduce the initial syndrome when they occur.

**Complications.** Muscular atrophy is not seen in the great majority of patients but may be present, particularly when the process has been of long duration. It most frequently involves the temporal, masseter, cervical, and proximal shoulder girdle muscles.

The patient with myasthenia is very susceptible to intercurrent infections, particularly respiratory ones, and tolerates even mild infections poorly. The sulfonamides and antibiotics have

reduced the serious effects of such infections when bacteria susceptible to the agents are responsible. Some female patients have a reduced fertility, but pregnancy does occur and may be followed by a normal delivery. Many remissions and an occasional relapse have been reported to accompany pregnancy. The children usually are entirely normal.

Respiratory insufficiency may develop quite abruptly or may be insidiously progressive. Of those complications which are the direct result of the disease, respiratory failure is the most common fatal one.

**Pathology.** In some cases numerous small split fibers and frequent collections of small round cells, presumably lymphocytes, are seen among the muscle fibers and around the small blood vessels. Other organs may also show numerous similar cells. In as many as 20 per cent of certain series of cases, tumors of the thymus have been found. These may be either benign or malignant. In most of the remaining cases, persistence of an unusually large or a hyperplastic thymus is found.

**Pathogenesis.** This disease now appears to be the result of a specific functional abnormality at the neuromyal junction. Normally, acetylcholine is released at the neuromyal junction when impulses are passed across it. Cholinesterase is normally present and hydrolyses the complex quickly. Physostigmine and neostigmine antagonize this activity. Conduction of nerve impulses from the motor nerve to the muscle syncytium is impaired in myasthenia gravis, with resulting weakness and paralysis. The exact nature of the defect at the neuromyal junction is not clear. The administration of curare, quinine, or the quaternary ammonium compounds produces a somewhat similar clinical picture even in normal individuals, and is very dangerous in myasthenics because of the aggravation of symptoms which results.

**Diagnosis.** The diagnosis usually is made without difficulty if one considers the possibility and carefully evaluates the history. The characteristic pattern of myasthenic fatigability is easy to demonstrate by having the patient make some repetitive movement. Particularly in severe cases where more or less complete paralysis exists, the dramatic improvement which follows the intramuscular administration of neostigmine in doses of 1 or 2 mg. is helpful in diagnosis. Many times a

patient who is unable to sit up, speak, or swallow will in the course of five minutes show completely normal activity. In mild myasthenics, quinine or curare may be used cautiously and in small dosage as a diagnostic tool to observe the abnormally great effect of even small doses. Bulbar palsies, thyrotoxic myopathy, anxiety states, and bulbar involvement in amyotrophic lateral sclerosis are most frequently confused with myasthenia gravis.

Thyroiditis may simulate this syndrome in a remarkable fashion, but the correct diagnosis is usually made by recognizing the associated symptoms and signs of thyrotoxicosis. However, myasthenia gravis not infrequently is complicated by thyrotoxicosis, which increases the diagnostic difficulty. The two disorders may be related in some as yet obscure fashion. Response to therapy may in the end be the most helpful sign.

**Treatment.** The management of these cases divides itself into two problems: the treatment of acute episodes of severe paralysis, and long-term management. Neostigmine is by far the most useful drug during acute attacks and should be given parenterally in doses of 1 mg. and in multiples of this amount until the desired degree of improvement has been attained or side reactions prohibit its use in increasing amounts. The most common side reactions are gastrointestinal and uterine cramps which may be partially controlled by the simultaneous administration of atropine.

Other problems during the acute episode are to protect the patient from hypostatic pneumonia and other infections and to watch for impaired respiratory exchange with resulting cyanosis and respiratory acidosis due to failure of respiratory excretion of normal amounts of carbon dioxide. At times a Drinker respirator or other mechanical device for maintaining respiratory exchange may be life-saving. If these complications are prevented, most patients experience a remission after a few weeks. As time goes on, relapse tends to occur and a slow general trend toward increasing severity of the disease may be apparent.

Mild cases may require no special medical attention except during relapse. In the slightly more severe case, neostigmine in oral doses of 15 mg. every two or three hours, or multiples of this dose, as needed, is the most useful medication and may be quite effective. Over a period of

months or years the dosage may have to be increased progressively until the cost becomes nearly prohibitive. The maximal effect of neostigmine given orally appears in half an hour and decreases rapidly after that time.

Supplementing neostigmine with ephedrine, guanidine, potassium salts, and glycine may have real value in certain cases, particularly in relieving the weakness which occurs between doses of neostigmine. The possible usefulness of these agents must be investigated for each patient.

Variation in the intensity of the disease at different times makes evaluation of any type of management extremely difficult. This statement is nowhere better demonstrated than in attempting to assess the results of thymectomy and radiation of the thymus. Although a few dramatic and apparently permanent cures have been effected by excision of the thymus, particularly where a thymic tumor has been found and removed, the

majority of patients continue to have symptoms of myasthenia after thymectomy. Some proponents of the procedure believe that only early, chronically active, but not too severe cases should be selected for operation. The postoperative management of these patients is difficult and requires oxygen, a respirator, parenterally administered neostigmine, and constant medical and nursing attention for a variable period up to a number of weeks. Because of the unpredictability of remissions, the relatively few examples of striking improvement and the great danger to the patient, thymectomy cannot be recommended as a routine procedure (see Chapter 64).

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### Thyrotoxic Myopathy

Frank H. Tyler

Thyrotoxicosis is usually associated with muscular weakness which is most marked in the large axial and thigh muscles. Sometimes these symptoms are the most striking or the presenting manifestations. This phenomenon is sometimes referred to as thyrotoxic myopathy. In severe cases atrophy of muscle tissue, which is very diffuse but seldom complete in any one muscle, occurs. The diagnosis is made by the finding of other symptoms, signs, and laboratory evidence of thyrotoxicosis. A search for evidence of thyrotoxicosis is indicated in any of the myopathies, because it can be satisfactorily treated. It is very gratifying to be able to bring about return of muscle mass and strength in a patient who has

been mistakenly regarded as having an incurable muscle disorder. Such cases may be managed by the administration of anti-thyroid drugs such as 6-N-propyl thiouracil or by subtotal thyroidectomy, if this is indicated. The therapeutic response is usually excellent if proper control of the excess thyroid activity is attained and the severe muscular disability has not exceeded a few months.

For further discussion, see Thyrotoxicosis, Chapter 55.

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## Familial Periodic Paralysis

Frank H. Tyler

Clinical Pattern  
Pathogenesis  
Treatment

**Clinical Pattern.** Familial periodic paralysis is a very rare disorder which occurs in certain families, usually being inherited as a Mendelian dominant. The clinical story is a striking one. The patients are normal except for well-demarcated episodes in which intense weakness or complete paralysis of voluntary muscles develops. The attacks begin in early life and may come at any interval throughout life, but are most frequently encountered in adolescence or early adult life.

A single attack may last from a few minutes to several days, although most are of 12 to 48 hours' duration. The attacks in many patients have a periodicity and duration which is characteristic of the individual or family. During the episode there is marked hypotonia of the muscles and hyperextensibility of the joints. The tendon reflexes are absent or greatly reduced, but return to normal as strength and tone return. The muscles are refractory to electric stimulation. The facial, pharyngeal, and respiratory muscles are affected only in very severe cases, but respiratory embarrassment and death have been reported.

The attacks are precipitated by many factors in individual cases, such as violent exercise or a large high-carbohydrate meal. At other times no apparent precipitating cause can be found.

There is no progressive muscular disease, and physical examination of a patient between attacks frequently demonstrates no abnormality.

**Pathogenesis.** The pathogenesis of certain cases has been elucidated. During the attack the serum potassium level drops sharply. This appar-

ently results from the sudden passage of potassium into the cells of the body, because the urinary excretion of potassium falls at the same time. The nature of the abnormality which causes this disturbance of the normal regulation of serum potassium levels is not known. Those attacks which follow large meals may be the consequence of the uptake of potassium by the liver as it stores glycogen.

The same clinical picture may be observed in patients with other disorders when serum potassium is depleted, as in severe diarrhea or in over-treatment with desoxycorticosterone of a patient with Addison's disease.

Reduction in serum potassium level, however, does not appear to be the mechanism responsible for the paralysis in certain patients whose disease is otherwise typical. The nature of the disorder in such cases is unknown.

**Treatment.** Episodes of paralysis are treated by the oral or intravenous administration of potassium salts in doses of 2 to 8 Gm. until the attack is relieved. Extreme care must be exercised in administering potassium salts by vein to patients, unless it is certain that a real deficiency exists. In appropriate cases a dramatic result is obtained. Normal renal function, sufficient fluids to maintain a good urine volume, and slow administration are the most important precautions which should be taken in giving potassium salts intravenously. In patients who have frequent episodes, attacks may be prevented by giving potassium chloride in dosage of 4 to 8 Gm. per day by mouth.

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## Section 5—Inborn Errors of Metabolism

### INTRODUCTION

An increasing number of disorders in the intermediary metabolism of various substances in the body are being discovered and their mechanisms elucidated. Some of these are relatively common and have been known for a long time, but in recent years much new light has been cast on the manner of their production. Others are rare and still not well defined. Hereditary factors play an important role in the etiology of a majority of

the disorders to be described. Some of these disturbances are manifest at birth and exist throughout life. Such disturbances are commonly termed "inborn errors of metabolism." Others appear later in life but show strong familial tendencies. Among those not hereditarily determined, the reaction to infection and other exogenous toxic agents plays the major etiologic role, but even in some of these the reaction may be dependent upon hereditary predisposition.

## 83

### Gout

George W. Thorn and Kendall Emerson, Jr.

History
Incidence
Etiology
Pathology
Clinical Picture
Acute Gout
Interval Gout
Chronic Gout
Complications
Diagnosis
Differential Diagnosis
Treatment
Acute Gouty Arthritis
Chronic Deforming Gouty Arthritis
Treatment of Interval Periods
Prophylaxis

**History.** Gout is a hereditary disturbance of uric acid metabolism first recognized medically by the ancient Greeks and Romans and deriving its name from the Latin word *gutta*, meaning "drop" in the joints. Clinical records characterizing the disease appeared in the writings of Aretaeus of Cappadocia, Caelius Aurelianus, and Hippocrates. Sydenham, a lifelong sufferer, differentiated gout from other arthritides. It was not until 1797, however, that it was realized that uric acid played a role in producing the symptoms. Wollaston and later Pearson made this important contribution. Fifty years later, Garrod demonstrated that the blood of patients with gout contained increased amounts of uric acid.

Further progress in the investigation of this disorder was made chiefly by the chemists Miescher, Kossel, Fischer, and Folin in their studies on purine metabolism.

**Incidence.** The incidence is not known. Hench reported that 5 per cent of all cases of joint disease seen at the Mayo Clinic have gout. Pathologic data show an incidence in the general autopsy population varying from 1 to 5 per cent. Certain factors seem to have a definite correlation with the disease incidence. In as high as 75 per cent of the cases studied at the Massachusetts General Hospital there was a familial incidence of the disease. Often there was a tendency to skip a generation, but it is of interest to note that hyperuricemia was a frequent finding in the asymptomatic kin of gouty patients. A single dominant gene is probably responsible for the transmission of asymptomatic hyperuricemia. In males this hyperuricemia is usually detected after puberty, and in females just before, or after, the menopause. The sex incidence of clinical gout favors the male, with only 5 per cent of cases occurring in the female. This may be related to the longer duration of hyperuricemia in the male. It has been suggested that in the female a serum

uric acid level of over 5 mg. per 100 ml. may indicate an abnormality in urate metabolism, and may compare with a level of 6 mg. per 100 ml. in males. If such a sex correction is introduced, the number of females with significant hyperuricemia

uric acid available for excretion is dependent upon endogenous breakdown of body proteins and upon exogenous or ingested purine and nucleoprotein. It has been determined that on a diet free of purines man normally excretes 300 to 600

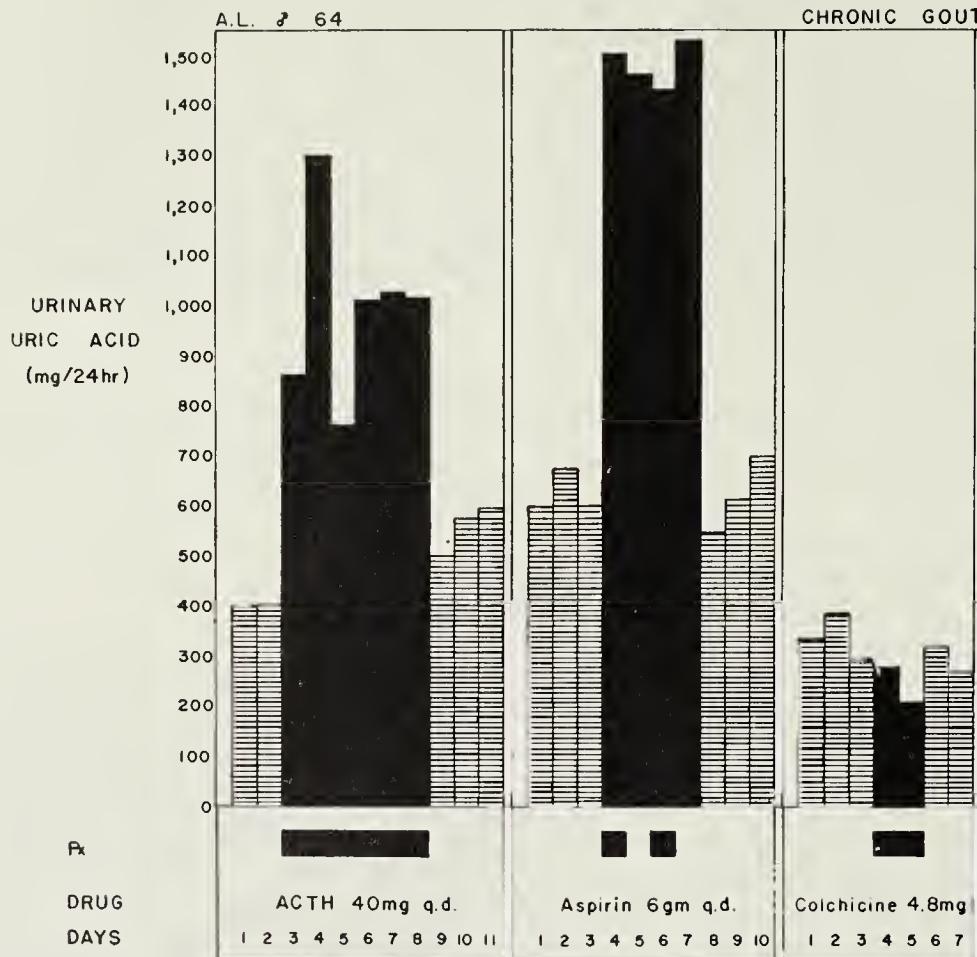


FIG. 135. Effect of various drugs on uric acid excretion.

is, of course, greatly increased. The age of onset varies from the second to the seventh decade. The greatest number fall in the fourth decade. Many factors have been incriminated in the precipitation of gout; however, there is no good evidence that "high living," Port wine, or racial factors play a significant role. Today it is obvious that the disease is not limited to "patricians."

**Etiology.** It is known that in man uric acid is the end product of purine metabolism. The purines are simple organic nitrogenous bases derived from the breakdown of nucleoproteins. These nucleoproteins are present in all living cells and are concentrated chiefly in cell nuclei, but occur to some extent in cytoplasm. In the process of hydrolysis the nucleoproteins liberate purines, such as adenine and guanine, which are subsequently deaminated and oxidized to form uric acid which in turn is excreted by the kidney. The

mg. of uric acid in 24 hours. It is of interest that uric acid is a threshold substance as far as renal clearance is concerned, and its excretion depends to a large extent upon the blood level. Reports have been collected to indicate that starvation, high-fat diet, exercise, lactic acid, ergotamine, atropine, and posterior pituitary solution decrease the excretion of uric acid. Mercury, aminophylline, epinephrine, cinchophen, large doses of salicylates, pituitary adrenocorticotrophic hormone (ACTH), and adrenal cortical steroids of the 11-17-oxysteroid type increase its excretion. It seems likely that many of these substances exert their effects, in part at least, upon renal tubular function. Colchicine does not appear to exert any effect on uric acid excretion (fig. 135).

Since hyperuricemia and urate deposits in the tissues are the fundamental chemical changes noted in gout, it would seem logical that one or

more of the three following mechanisms must be at fault:

1. Increased production of uric acid.
2. Decreased destruction of uric acid.
3. Inadequate excretion of uric acid.

It is difficult to obtain clear-cut data on the first point (i.e., increased production of uric acid), since by the time the disease is evident clinically there has already occurred a large increase in urate deposits in the body and an increased level of serum uric acid. Both of these factors should tend to increase the quantity of uric acid excreted on a purine-free diet, if some degree of renal insufficiency were not present. Even without renal insufficiency, uric acid clearance in gouty individuals with high acid levels is lower than in individuals with hyperuricemia due to other causes. This retention of uric acid in the blood and tissues is associated with an increased protein-bound and a diminished free uric acid fraction in the blood. However, impaired kidney function is most certainly an important factor in accelerating the course of the disease and as a cause of death.

It would not appear that decreased destruction of uric acid was a mechanism causing gout in humans, since up to the present there is no evidence that any appreciable degree of uricolytic occurs in the human. Thus far, studies using intravenously injected  $N^{15}$  uric acid reveal that: (1) in normal subjects, the rate of formation of uric acid exceeds the rate of urinary excretion by 20 per cent or more; and (2) in the gouty subject, the body uric acid pool may be up to 15 times larger than in the normal (fig. 136). It is quite probable that further studies with isotopic uric acid and purine substances will do much toward the elucidation of the mechanism responsible for the disturbance in uric acid metabolism.

**Pathology.** The pathognomonic lesion is the deposit of sodium urate crystals with resultant inflammatory and later degenerative reactions. These changes occur chiefly in joints, bones, bursae, and cartilaginous structures. Any or all joints may be involved, although usually those of the lower extremities, chiefly the great toe, are favored. Urate precipitates are seen in the articular cartilage and periarticular structures, with bone destruction, narrowing of the joint, degenerative changes in the synovium, bony ankylosis, and exostoses. The precipitates in other tissues are called *tophi*, meaning chalk stones. The helix

and antihelix of the ears, the tendons, the tarsal plates of the eyes, and the olecranon and patellar bursae may all be involved. The kidney, on its cut surface and in its collecting tubules, often shows urate deposits. These are usually related

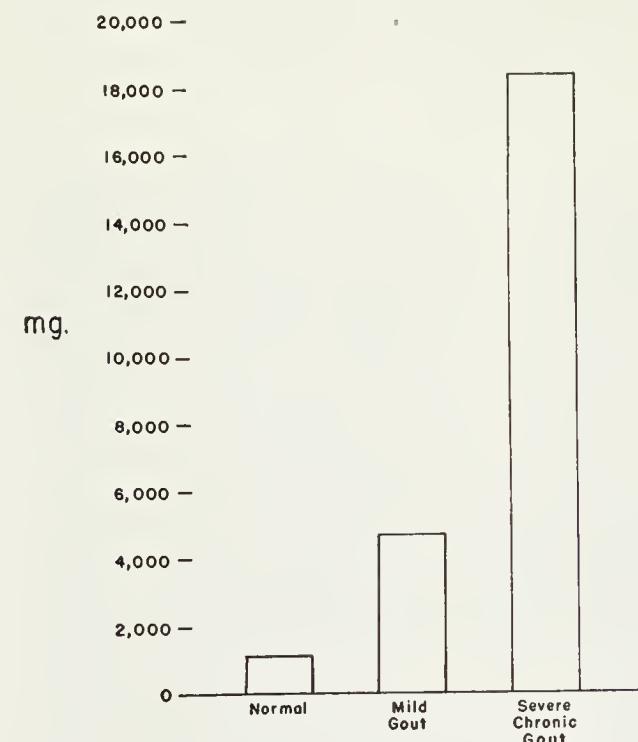


FIG. 136. Uric acid pool in normal and gouty subjects.

to the duration and severity of the gout. The glomeruli show varying degrees of fibrosis, and some arteriolar and arterial sclerosis of the renal vessels is invariably present. In addition, hypertension is present more frequently in this group than in others of a comparable age, and cardiac hypertrophy and arteriosclerosis are observed.

**Clinical Picture.** The evolution of gout clinically may be very slow, and often is unrecognized as such by the physician. It is characterized by acute attacks with intervals of complete well-being. Later the asymptomatic intervals become shorter, and finally a chronic deforming state persists. It is of interest that preceding the onset of the acute attacks there is almost always some traumatic episode—i.e., physical trauma, acute infection, surgery, exposure to cold, or injection of foreign proteins or drugs such as mersalyl, epinephrine, ergotamine, or liver extract. Interest in the relation of allergenic insults to gouty attacks has recently been revived.

**ACUTE GOUT.** The first sign of the disease in most cases is an acute arthritis. Renal colic may occasionally be the initiating episode. The meta-

tarsal-phalangeal joint of the great toe is frequently the first joint involved (fig. 137). This was true in 60 per cent of the cases seen by Scudamore in a study of 516 patients. In 27 cases, both great toes were involved initially. Other joints most frequently involved include the instep, ankle, heel, knee, and hand, respectively. The attack often occurs several hours after midnight, awakening the patient from sleep. Classically, the joint is swollen, tender to touch, excruciatingly painful, and a cyanotic violaceous color. Lymphangitis and true cellulitis are rarely present. There may be monarticular or migratory polyarticular involvement. The patient complains of general malaise, headache, and tachycardia. The temperature often rises to 104° F., and is associated with an elevated leukocyte count and erythrocyte sedimentation rate. The serum uric acid level is elevated, and the urinary volume is small. Abnormally low 17-ketosteroid excretion has been noted during acute gouty arthritis and asymptomatic interval gout. Preceding the attack, and occasionally at its peak, a diuresis of sodium, chloride, and uric acid occurs. The acute episode may last a few days to a week, but may last

several weeks in very severe cases. Duration of an attack depends largely upon the initiation and adequacy of therapy. All acute symptoms may subside, and, aside from some desquamation over the involved sites, no permanent impairment of the joints may occur. One case reportedly developed ankylosis of the joint following the first attack. This is extremely rare.

**INTERVAL GOUT.** The interval between acute attacks varies from months to years. During this time the patient is symptom free. As the disease progresses, the intervals become shorter. Vigilance during these periods and prompt treatment of any suggestive activity determine to a great extent not only the frequency and severity of acute attacks, but the development and progression of a chronic gouty arthritis.

**CHRONIC GOUT.** The diagnosis of chronic gout is made after the patient has had recurrent acute attacks culminating in deforming changes in the joints. Urates are deposited in the joint spaces, capsules, tendons, bursae, and skin. The latter are often referred to as "gravel of the skin." In this phase, sinuses develop which drain chalky white material. Many joints are ankylosed. Two per cent of the cases seen at the Massachusetts General Hospital became bedridden and crippled by the disease.

**Complications.** Complications of the disease include slowly progressive renal impairment with azotemia resulting in death before the age of 50. In 73 of 77 cases of gout seen at autopsy by Gudzent, marked renal impairment was found. Occasional cases of urate calculi with colic occur.

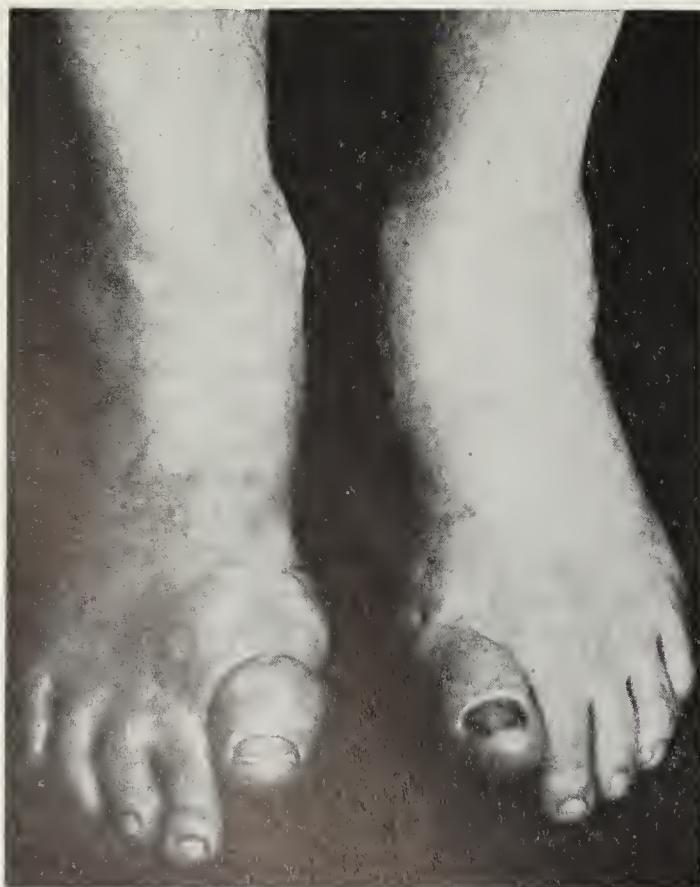


FIG. 137. (*Left*) Appearance of feet in chronic gout. Note swelling of the great toes and subcutaneous deposits of uric acid opposite the first metatarsal joint. (*Right*) Appearance of hands in chronic gout. Note joint enlargement due to deposits of uric acid.



Complications such as hypertensive cardiovascular disease of the benign variety with generalized arteriosclerosis have been shown to occur frequently in young patients with gout. Two per cent of patients show muscular atrophy associated chiefly with badly deformed joints and impaired motion. Certain diseases appear to be associated with gout more often than one would expect simply by statistical chance. These include diabetes mellitus, leukemia, polycythemia vera, pernicious anemia, and Paget's disease. In some of these, an increased breakdown of cellular nuclei may account for the association. In others, no obvious relationship has been established.

**Diagnosis.** The diagnosis of gout is simple to establish in the presence of an acute attack, but more difficult in the chronic stage of the disease. Several factors in the history, physical examination, and chemical findings are helpful in making the diagnosis. These include a family history of gout or hyperuricemia, urate calculi, the onset of acute attacks following traumatic episodes, classic picture of acute arthritis, an elevated serum uric acid level in the absence of severe renal disease, and finally a satisfactory response of the acute arthritis to colchicine medication. Simultaneously with a serum uric acid level analysis, one should always determine the blood urea nitrogen or the nonprotein nitrogen to differentiate hyperuricemia associated with gout from hyperuricemia secondary to renal disease. In the latter the elevation in blood urea nitrogen or nonprotein nitrogen will be much greater for a given elevation in serum uric acid level (table 83). Subsequent

contents of sodium urate confirmed by the muricide test. (Heat chalky contents in dilute nitric acid and evaporate to dryness. Cool and add ammonia solution. If the test is positive, a purple-red color develops which, under the microscope, reveals needle-like crystals of sodium nitrate.) The bone x-ray findings are often similar to those seen in rheumatoid arthritis, sarcoidosis, syphilis, and hyperparathyroidism (fig. 138). There may



FIG. 138. X-ray of a foot in a case of chronic gout. Note marked destruction of the first and second metatarsal joints and adjacent punched-out areas of diminished density.

be evidence of swelling around the joint in the acute phase, or punched-out areas in the bone near the involved joints, as well as joint changes with ankylosis and decreased density by x-ray.

**Differential Diagnosis.** Acute arthritis must be differentiated from acute rheumatic fever, rheumatoid arthritis, osteoarthritis, gonorrheal arthritis, and acute cellulitis. The finding of an elevated serum uric acid and the response to colchicine rule out all of these conditions and confirm the diagnosis of gout.

Table 83

COMPARISON OF SERUM URIC ACID AND BLOOD UREA NITROGEN LEVEL IN PATIENTS WITH GOUT AND NEPHRITIS

	Normal	Gout	Nephritis
Serum uric acid (mg./100 ml.)	2-5	8	6
Blood urea nitrogen (mg./100 ml.)	8-15	15	45

*complete and rapid disappearance of all symptoms of arthritis is strong evidence in favor of an attack of acute gouty arthritis.*

The pathognomonic finding of the disease is the tophus which on aspiration reveals chalky

Traumatic joint injuries may be differentiated from gout by a careful history of the nature of the injury. An acutely painful joint following a minor or trivial injury suggests gout, whereas a forceful injury with moderate pain and swelling is compatible with changes following acute stress. Acute arthritis occurring during the first few days following operation should always suggest gout. There is a form of palindromic arthritis in women which suggests gout because of its recurrent nature and the complete disappearance of joint manifestations between attacks. Gout is unusual in women, and when it occurs is frequently associated with renal disease such as chronic glomerulonephritis and pyelonephritis.

**Treatment.** For the most part, the physician is called upon to relieve acute gouty arthritis or renal calculi or to ameliorate the symptoms of chronic deforming gouty arthritis and azotemia secondary to progressive renal involvement. In advanced cases it is necessary to treat a chronic deforming gouty arthritis.

**ACUTE GOUTY ARTHRITIS.** The principles of therapy are:

1. Bed rest with early and complete rest of the affected joints.
2. Relief of pain with colchicine, salicylate, or codeine.
3. Fluids to correct dehydration and increase elimination of uric acid.
4. High-carbohydrate, low-fat, low-purine diet.

The afflicted joint should be put at rest at the onset of acute symptoms. Motion should be resumed as soon as this can be accomplished without pain. In this respect the treatment of gouty arthritis differs from the prolonged rest frequently recommended in other types of arthritis. The symptomatic response of acute gouty arthritis to the use of colchicine is both dramatic and diagnostic. The standard preparation is a tablet which contains 0.5 mg. of active material. The pharmacologic action of colchicine in gouty patients is not known. It has been definitely established, however, that it does not act by increasing the urinary excretion of urate. Colchicine therapy should be instituted with the onset of acute arthritis symptoms or the prodromata. One tablet, 0.5 mg., should be taken every hour until pain is relieved or gastrointestinal disturbances, including diarrhea, force its discontinuance. Patients soon learn from experience the

optimum number of tablets which are necessary. Once treatment has been started, colchicine therapy should be continued throughout the day and night until relief is afforded. Subsidence of joint pain is noted in most instances after 12 hours of medication.

Acetylsalicylic acid may be given in amounts up to 2 to 5 Gm. daily. It is a helpful analgesic and in addition promotes the excretion of uric acid. Codeine phosphate, in doses of 30 to 60 mg., may be given in more severe cases in conjunction with colchicine and salicylates. Morphine or "Demerol Hydrochloride" may be required in severe cases, but should be used cautiously in patients with a chronic, painful disease. An abundant fluid intake is important and may often be combined advantageously with a high carbohydrate intake and salicylate therapy.

Recently the use of adrenocorticotrophic hormone (ACTH) has been reported to increase uric acid excretion and, on continued administration of 40 to 100 mg. daily, to result in steady improvement in acute gouty arthritis. Remissions may occur following the sudden cessation of therapy, if the course of treatment is inadequate. To some extent this reaction may be obviated or modified by slowly reducing the dose of hormone before discontinuing therapy completely.

**CHRONIC DEFORMING GOUTY ARTHRITIS.** Low-grade symptoms may persist and may be interspersed with acute attacks of gouty arthritis. Colchicine and salicylates are particularly useful in the treatment of gout at this stage. One or two tablets of colchicine (0.5 to 1 mg. daily) may be taken continuously, and 1 to 3 Gm. of acetylsalicylate daily. Cinchophen is extremely useful in patients who fail to respond to the aforementioned therapy. It is a relatively safe drug if care is used to be certain that the liver function is normal and that an adequate diet of high carbohydrate content is taken in conjunction with cinchophen therapy (0.5 Gm. three times daily for three days a week for two to six weeks). Surgical treatment may be employed to remove large, painful subcutaneous tophi, discharging sinuses associated with a tophaceous deposit, and extensive osseous involvement of the fingers and toes. ACTH, pituitary adrenocorticotrophin, in doses of 10 to 25 mg. every sixth hour, will often terminate an acute or chronic gouty attack dramatically. However, sudden withdrawal of the hormone may precipitate a further attack. Long-

continued administration of ACTH or cortisone, while capable of alleviating the symptoms of gout, may, of course, lead to signs of hyperadrenocorticism (Cushing's syndrome) and possibly to other side effects involving the central nervous system. It is possible that small doses of ACTH for short periods of time in conjunction with colchicine or salicylates may prove to be very beneficial in cases resistant to other forms of medication. The ultimate usefulness of adrenocorticotropic hormone (ACTH) or cortisone in chronic gouty arthritis has not been established with certainty, but justifies serious consideration.

The treatment of azotemia associated with chronic gouty nephritis is identified with that discussed under Chronic Nephritis with Uremia (see Chapter 19).

**TREATMENT OF INTERVAL PERIODS.** In contrast to the very minor differences observed among experts in the form of therapy recommended for the acute gouty attack, there is widespread difference concerning the usefulness of many forms of therapy employed in an effort to prevent the onset of clinical manifestations of gout in patients with long-standing hyperuricemia or in preventing recurrences of acute or chronic gouty episodes. In the absence of conclusive evidence one way or the other, the author feels that, since gouty manifestations appear ultimately to be due to the retention of large quantities of urate, a program designed to limit the ingestion of purine and to facilitate the loss of urate from the body should, over a period of months or years, reduce the disability occasioned by the progressive nature of the disease. It is to be recognized that any type of stress such as hard exercise, trauma, fever, operation, and injury may precipitate an attack of acute gouty arthritis. Prevention of an attack will depend in part, therefore, upon the ability of patients to avoid such situations. A large fluid intake is helpful in eliminating uric acid from the body, in preventing renal calculi, and in retarding the progressive involvement of the kidneys. A high-carbohydrate diet increases uric acid excretion; whereas a high-fat diet tends to decrease uric acid excretion and may, in some patients, precipitate gouty attacks. Only those protein foods containing nucleoproteins whose end product of metabolism is uric acid need be considered in dietary management. It would appear wise, there-

fore, in attempting to prevent attacks of gout to ingest large quantities of fluid, and a diet of high carbohydrate, low fat, and low purine content. Restricting a diet to 100 mg. of purine per day permits a 3-ounce serving of meats, fish, sea foods, beans, peas, and lentils. There should be no necessity for restricting at all those foods containing less than 15 mg. of purine per 100 Gm. On the other hand, those foods of exceptionally high purine content should not be included at all (table 84).

Table 84  
PURINE CONTENT OF FOOD

Group A (150-800 mg.)	Group B (50-150 mg.)	Group C (0-15 mg.)
Sweetbreads	Meats	Vegetables
Anchovies	Fish	Fruits
Sardines	Sea foods	Milk
Liver	Beans	Cheese
Kidneys	Peas	Eggs
Meat extracts	Lentils	Cereals
High purine content not allowed	Restricted to one serving per day	Low purine content, unlimited quantities allowed

The excretion of uric acid may be facilitated by the administration of salicylates in doses of 5 to 6 Gm. once a week, or with cinchophen, provided liver function is normal and a diet adequate in all respects is ingested. It is desirable not to permit patients to ingest alcohol when cinchophen therapy is being administered. Cinchophen may be given according to the plan of Graham—i.e., 0.5 Gm. three times a day for three days a week, the dose being reduced after four to six weeks to two days a week, finally to one, and then omitted entirely. Patients who are obese should be placed on a diet to restore their normal weight, although it must be recognized that during the period of weight reduction acute attacks of gout may occur. *Under no circumstances should the caloric intake of the high-carbohydrate diet be such as to increase the weight of a patient above his ideal.* Since gout occurs primarily in individuals over 50, and since many are obese and may have in addition a family history of diabetes, the development of diabetes mellitus during the course of gout should be anticipated. Particularly is this true in patients on a high-carbohydrate regimen. According to Bartels, indisputable benefit was obtained in a group of patients with gout who

carefully adhered to a low-fat, low-purine, high-carbohydrate diet with the addition of decreasing doses of cinchophen. On this plan of treatment the number of attacks of gout was reduced to one-tenth that which had occurred during the year prior to treatment.

**Prophylaxis.** All male children of gouty patients should be checked carefully for hyperuricemia. It is apparent that only a small percentage of young males with hyperuricemia will develop clinical evidence of gout. It seems evident, however, that the majority of patients with gout will be derived from this group. Under such circumstances, it would appear desirable to attempt to prevent or delay the onset of gout by instituting at an early age, in the presence of hyperuricemia, some restriction of purine intake (100 mg. per day maximum) and by encouraging the ingestion of fluid sufficient to provide at least

2 liters of urine daily. By prolonged adherence to such a program, it may be possible to reduce the rate at which urates accumulate excessively in the body tissue; and, in so far as this contributes to clinical gouty manifestations, one should delay the onset of arthritis and nephritis. However, to date, conclusive studies on this point are not available.

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## 84

### Hemochromatosis

George W. Thorn and Kendall Emerson, Jr.

History  
Incidence  
Etiology  
Pathologic Physiology  
Clinical Picture  
Diagnosis  
Prognosis and Treatment

Hemochromatosis is a disease characterized by excessive deposits of iron in the body, particularly in the liver, pancreas, and other parenchymal tissues, and by the presence of hepatic cirrhosis and diabetes mellitus (bronze diabetes).

**History.** The first clinical description of the disease was given by Hanot and Chauffard in 1892. In 1889 von Recklinghausen named the disease hemochromatosis and described the two pigments hemosiderin, an iron-containing compound, and hemofuscin, a substance devoid of iron.

**Incidence.** Hemochromatosis is a rare disease, found in about 0.1 per cent of autopsies. Sheldon, in 1935, summarized the literature, noting a total

of 311 cases reported between the years 1865 and 1935. It is a disease occurring chiefly in the fifth and sixth decades. Approximately one half of Sheldon's cases occurred between the ages of 45 and 55. Ninety-five per cent of the patients were males.

**Etiology.** The nature of the disturbance in iron metabolism in hemochromatosis is not known. Since it appears, however, that iron is not excreted in appreciable amounts even in normal individuals, there must be an increased absorption of iron in this condition. Direct evidence of this has recently come from studies in which 20 per cent of a test dose of ferrous iron given orally to a patient with hemochromatosis was retained, whereas normal persons retain 2 per cent or less of such a dose. The work of Hahn and his associates indicates that, normally, the gastrointestinal mucosa regulates iron absorption. (The recent studies of Endicott suggest that appreciable

quantities of iron may be lost through perspiration.) In South African natives on poor diets, Gilman and Gilman have found excessive iron deposits comparable to those seen in hemochromatosis. Experimental work in animals indicates, likewise, that on diets low in phosphate excessive amounts of iron may be absorbed and stored in the liver. It does not appear that dietary factors are responsible in the sporadic types of hemochromatosis, but the character of the iron deposits is strikingly similar. Cases have been reported in which the typical clinical picture of hemochromatosis has been produced by parenteral administration of iron in the form of repeated blood transfusions. It seems possible that the striking difference in incidence between men and women may be explained partly by the relatively large quantities of iron lost by women through menstruation and pregnancy. Females with hemochromatosis are almost invariably past the menopause.

**Pathologic Physiology.** The total body iron of 4 to 5 Gm. may be increased tenfold. Quantities of iron equal to 20 Gm. or more may be found in the liver in hemochromatosis, in contrast to a normal tissue iron content of less than 1 Gm. The iron is found also as hemosiderin deposits in the pancreas, skin, thyroid, myocardium, and the secretory tissues of the body. Interestingly, the spleen and bone marrow contain relatively little of the pigment. Whether the fibrosis of liver and pancreas is attributable to the iron pigment is not certain, but seems probable. The initial necrosis is confined to the pigment-containing cells, and the degree of progression and extension of the cirrhotic process is proportional to the amount of pigment deposited in the various organs.

**Clinical Picture.** The symptomatology is related to the skin pigmentation, hepatic cirrhosis, and diabetes. Of these only the cirrhosis appears to be constant. The skin is usually dry and scaly. Abnormal skin pigmentation has been reported in about 80 per cent of the cases, either as diffuse bronzing or as a slate gray metallic tint. In about half of the cases the skin pigmentation is due to melanin, and in the other half it is due to deposits of iron. It is quite probable that the increased melanin deposition represents a change secondary to the hepatic cirrhosis so frequently observed in contrast to the primary deposition of iron pigment in the skin. The mucous membranes

are pigmented in about 16 per cent of the cases. Although the whole body may be affected, the extensor surfaces of the lower forearms and dorsum of the hands are usually the most deeply pigmented. Most frequently the first symptoms relate to hepatic involvement. In the early stages of the disease, the liver was palpable in 92 per cent of the cases summarized by Sheldon, and the spleen enlarged in 60 per cent. Dull epigastric pain and ascites were occasionally present. Jaundice and hematemesis were rare. Diabetes was present at death in three fourths of the cases, although in the early stages of the disease it is rarely seen. Insulin resistance is not infrequently found, and, of the 24 patients studied by Joslin, 13 required more than 50 units of insulin per day.

Genital hypoplasia, impotence, and loss of secondary sex characteristics may be marked. Since involvement of testicular tissue by the process may occur early, hypogonadism may be one of the first evidences of the disease. Complete heart block and cardiac failure attributed to iron deposits in the heart have been reported. In approximately 10 per cent of patients carcinoma of the liver develops, secondary to cirrhosis. Frequently cases are recognized only at autopsy, being relatively asymptomatic until an intercurrent infection produces coma and death.

**Diagnosis.** Since there may be nothing distinctive regarding the hepatic and pancreatic disease, the diagnosis depends on the demonstration of excessive deposits of iron. While liver biopsy is the only infallible method, other technics are useful. These include: skin biopsy or the injection of acidified potassium ferrocyanide subcutaneously to demonstrate iron; an elevated serum iron level with saturation of the iron-binding (siderophilous) protein of the serum; deposits of hemosiderin in the cells of the urinary sediment; and occasionally increased iron in the marrow by sternal puncture. The technics which demonstrate excessive iron are valid diagnostic procedures for hemochromatosis in the absence of those types of anemia associated with a disturbance in iron metabolism. Diabetes with pigmentation (associated with hypogonadism) should always suggest the diagnosis. In some cases the diagnosis may be established by the demonstration of an abnormally dense liver shadow on the x-ray film caused by the excessive concentration of iron in the liver.

Hemochromatosis should not be confused with hemosiderosis in which hemosiderin may be deposited in the spleen, liver, and reticuloendothelial system as a result of chronic blood destruction associated with such conditions as hemolytic anemia and malaria. Similar extensive hemosiderin deposition may occur in the pulmonary lymphatics in congenital or rheumatic heart disease associated with pulmonary hypertension and chronic passive congestion of the lungs. This occurs as the result of the breakdown of blood extravasated from the pulmonary capillaries. Since hemosiderin is radiopaque, x-ray of the lungs gives a characteristic picture.

**Prognosis and Treatment.** The average duration of life after diagnosis is approximately two years. This relatively short life expectancy, as reported by Sheldon, is due in a large part to the high diabetic mortality prevailing in the pre-insulin era. At the present time, the liver disease probably contributes the greatest hazard to the patient, and careful dietary management and

vitamin supplements are indicated. Recent studies have shown that it is possible to bleed patients with hemochromatosis repeatedly, thus removing iron from the increased tissue stores. If increased iron deposition is responsible for hepatic and pancreatic lesions, it may be possible to improve both liver and pancreatic function by weekly phlebotomies in cases without high-grade cirrhosis or permanent fibrotic changes. A diet high in phosphates will, by producing highly insoluble iron complexes, limit iron absorption.

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## 85

### Amyloidosis

George W. Thorn and Kendall Emerson, Jr.

History  
 Incidence  
 Etiology  
 Pathology  
 Clinical Picture  
 Diagnosis  
 Treatment

**History.** The widespread deposition of a homogeneous material throughout many organs of the body was first described in 1842 by Rokitansky. Virchow, in 1854, noted that, like starch, this material stained blue with iodine and sulfuric acid, and termed it *amyloid*. Actually it has no relation to starch but is a *protein* of variable composition usually associated with a *sulfate-bearing polysaccharide* similar to, if not identical with, chondroitinsulfuric acid.

**Incidence.** Amyloidosis may be divided into primary and secondary types. Primary amyloid-

dosis is of unknown etiology and rare occurrence; secondary amyloidosis is much more frequent and is associated with a chronic suppurative or inflammatory process such as tuberculosis, bronchiectasis, osteomyelitis, or rheumatoid arthritis. The two types also differ characteristically in the predominant localization of amyloid deposits in the various body tissues (table 85). A third type of amyloidosis is associated specifically with multiple myelomatosis. It resembles the primary type in its localization, but occurs more frequently in bones, joints, tendons, and muscles.

**Etiology.** The etiology of amyloidosis is uncertain. Experimentally, it may be induced by the repeated injection of sodium caseinate or by hyperimmunization with bacterial vaccine. It is generally considered that secondary amyloidosis

results from the storage in the reticuloendothelial system of abnormal or incomplete protein breakdown products arising from areas of tissue damage or destruction. It is possible that these protein breakdown products may constitute antigen-antibody complexes.

Table 85

## LOCALIZATION OF AMYLOID DEPOSITS

Location	Per Cent of Cases	
	Primary Amyloidosis*	Secondary Amyloidosis†
Heart.....	85	1
Tongue.....	57	1
Gastrointestinal tract.....	52	4
Skeletal muscle.....	41	..
Kidney.....	26	72
Spleen.....	24	89
Adrenal gland.....	22	41
Liver.....	17	63
Bone and joint.....	11	..

\* Data from Eisen: *Am. J. Med.*, **1**:144, 1946 (46 cases).

† Data from Rosenblatt: *Am. J. M. Sc.*, **186**:558, 1933 (110 cases).

**Pathology.** Amyloid is deposited initially around small blood vessels and from this point it spreads gradually throughout the connective tissue stroma, encroaching upon and choking off the parenchymal cells in its path. The material is identified by its staining affinity for Congo red, iodine and sulfuric acid, or methyl violet. Secondary amyloid deposits nearly always stain characteristically with all three dyes, whereas primary amyloid and that associated with multiple myeloma may take only one or two of these dyes, and then much less intensely.

**Clinical Picture.** The signs and symptoms of amyloidosis depend entirely upon the organs involved. The liver and spleen may be enlarged, with signs of hepatic insufficiency. Kidney involvement produces the picture of nephrosis with eventual renal failure and death, often with-

out hypertension. Amyloid deposition in the heart and lungs may result in cardiac and pulmonary insufficiency. Elsewhere there may be only local painless enlargement of an organ such as the tongue or thyroid, or visible infiltration of areas in the skin.

**Diagnosis.** Amyloidosis should always be looked for in the presence of any long-standing suppurative or inflammatory process, especially when there is an elevation of the serum globulin. Congo red is taken up by amyloid, and if over 80 per cent of a standard dose of 10 ml. of a 1-per cent solution of this dye disappears from the blood within one hour after intravenous injection, there is strong presumptive evidence for the presence of amyloidosis. In the presence of proteinuria the dye may appear in the urine and give a false positive test which is detected by acidifying the urine and noting the characteristic color change to blue of Congo red. A negative test does not rule out amyloidosis, since considerable quantities of amyloid must be present in order to retain a sufficient amount of dye to give a definitive test. Furthermore, certain types of amyloid appear not to have an affinity for Congo red. Under these circumstances a diagnosis may be established only by biopsy.

**Treatment.** The treatment of secondary amyloidosis should first be directed at the associated condition, cure of which may or may not be followed by disappearance of the amyloidosis. Remarkable benefit from the use of raw liver orally and crude liver preparations parenterally has been described recently; the amyloidosis may disappear in a matter of months even though the underlying disease process is unchanged.

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## Disorders of Amino Acid Metabolism

George W. Thorn and Kendall Emerson, Jr.

Cystinuria  
Alkaptonuria  
Phenylpyruvic Oligophrenia  
Histidinuria  
Tyrosinosis  
Fanconi Syndrome  
Hepatolenticular Degeneration (Wilson's Disease)

### CYSTINURIA

**Definition.** Cystinuria is a rare inborn error of metabolism in which large quantities of cystine are excreted in the urine—i.e., 0.4 to 1.0 Gm. daily in contrast to the normal quantity of less than 0.1 Gm. daily.

**Incidence.** The disorder affects both sexes, possibly more males, and may occur at any age. Cystinuria has been observed among several members of a single family, and under such circumstances follows the pattern of a recessive Mendelian characteristic.

**Etiology.** That the excessive excretion of cystine in the urine is not primarily exogenous but also endogenous in origin is indicated by the fact that on a protein-free diet or in starvation the cystinuria persists. On the other hand, the feeding of high-protein diets increases the degree of cystinuria. Under such circumstances, methionine and cysteine, being cystine precursors, are excreted largely as extra cystine in the urine. The defect appears to be related to an inability of the liver to oxidize cysteine to cystine. Cysteine, therefore, is carried to the kidneys, oxidized to cystine, and excreted as such or deposited as crystals. When cystine is fed to the patient, however, since it is in an already oxidized state it is further metabolized to sulfate by the body and is not excreted as cystine.

**Clinical Picture.** Cystinuria, *per se*, is symptomless; but, since cystine is one of the more insoluble amino acids, crystals and calculi often form, usually in patients passing an acid urine. Cystine crystals may also be deposited throughout the organs of the body. Cystinuria is not diagnosed in most instances until renal calculi have developed. Cystine lithiasis occurs in approximately 2 per cent of cystinuric patients.

The stones are frequently multiple and bilateral and reveal increased density by x-ray. They tend to recur because of the underlying persistent cystinuria.

**Diagnosis.** Careful microscopic examination of the urine sediment will reveal characteristic hexagonal cystine crystals. To confirm the diagnosis a simple chemical test can be done on the first morning sample of urine, as follows:

To 5 ml. of urine made alkaline with ammonium hydroxide, 2 ml. of 5 per cent sodium cyanide solution is added and allowed to stand for from 5 to 10 minutes; a few drops of a freshly prepared 5 per cent sodium nitroprusside solution is then added; in the presence of cystine, a permanent deep purplish red will develop.

**Treatment.** The inborn error in metabolism cannot be corrected. However, a low-protein, alkaline ash diet with high carbohydrate and fat intake will reduce the total quantity of cystine excreted. Cystine solubility increases greatly in alkaline urine, and continued alkalinization is thus highly desirable to prevent further calculus formation. Sodium citrate, 3 Gm. three or four times daily, is helpful. Each voided urine specimen should be alkaline by simple pH paper tests. Cystine stones often will respond satisfactorily to bladder or renal pelvis lavage. Although cystine calculi appear to be the most amenable of all urinary calculi to medical therapy, surgery often is required.

### ALKAPTONURIA

**Definition.** Alkaptonuria is a rare inborn error of metabolism affecting the intermediary metabolism of phenylalanine and tyrosine, which gives rise to the excretion of homogentisic acid in the urine.

**History.** Maracet in 1823 described the clinical manifestations of the disease. The nature of the abnormal reducing substance in the urine was recognized by Marshall in 1887.

**Incidence.** Less than 200 instances of the disease have been reported. It occurs more

frequently in males than in females, and appears to be inherited as a recessive Mendelian characteristic.

**Etiology.** Present knowledge suggests that alkapttonuria is related to a defect in the mechanisms by which homogentisic acid is oxidized. Homogentisic acid given to normal persons is not excreted in the urine. Alkaptonuria is aggravated by the administration of either phenylalanine or tyrosine. It has been shown that the intramuscular injection of liver will free the urine of homogentisic acid for several hours following injection. Significant quantities of homogentisic acid occur in the urine of normal subjects following the administration of *l*-tyrosine. With large doses of vitamin C, the excretion of homogentisic acid ceases. Although vitamin C appears to correct the experimentally induced alkapttonuria, it has little effect on the hereditary type.

**Clinical Picture.** In most cases the condition is present at birth and continues throughout life, although a few cases of intermittent alkapttonuria have been recorded. Patients with alkapttonuria exhibit no symptoms. The diagnosis is suggested early in life by the dark stains from urine upon diapers and linen. Such urine, upon standing and becoming alkaline, gradually turns brown to black in color with the oxidation of homogentisic acid.

The disease is benign for many years. After the age of 40, however, alkapttonuric individuals may develop secondary ochronosis which often leads to crippling osteoarthritis. Since the blood of alkapttonuric patients may show fixation of complement, in patients with this disorder the interpretation of a positive complement-fixation test is open to question.

**Diagnosis.** The development of dark brown or black urine on standing is characteristic. The addition of 10 per cent sodium hydroxide solution to urine with homogentisic acid results in formation of a black precipitate. If a drop of urine, first made alkaline with sodium hydroxide, is placed upon sensitized photographic paper, the paper will immediately turn black if homogentisic acid is present (hydroquinone reaction). Alkalization of the urine with oxidation of homogentisic acid is followed by chemiluminescence which may be observed easily in a dark room.

*Since homogentisic acid reduces alkaline copper solutions, glycosuria may be mistakenly diagnosed.*

However, homogentisic acid is not fermented by yeast.

**Treatment.** Nitrogen balance may be improved and homogentisic acid excretion reduced by administering a diet restricted in protein but high in carbohydrate and fat. Large doses of vitamin C—i.e., 500 mg. daily—may be tried. The possible beneficial effect of liver extract given daily for prolonged periods warrants study.

## PHENYL PYRUVIC OLIGOPHRENIA

This is an inborn error of metabolism associated with the constant excretion of phenylalanine and its derivatives, phenylpyruvic acid and phenyl-lactic acid. It is always associated with mental defectiveness.

**History.** Fölling, in 1934, first reported the occurrence of phenylpyruvic acid in the urine of certain mentally defective individuals. This was subsequently confirmed by Penrose in England and by Jervis in the United States.

**Incidence.** Excretion of appreciable quantities of phenylpyruvic acid, a derivative of phenylalanine, has not been observed in otherwise normal individuals. An incidence of approximately 0.5 per cent of phenylketonuria has been reported among the population of institutions for mental defectives. The defect appears to be congenital and familial, and to be inherited by a single Mendelian recessive characteristic.

**Etiology.** The administration of phenylalanine, phenylpyruvic acid, or phenyl-lactic acid leads to an increased excretion of phenylpyruvic acid. The feeding of other amino acids, including tyrosine, does not augment the excretion of phenylpyruvic acid. The defect apparently resides in the reactions by which phenylalanine usually is converted to tyrosine. Patients with phenylpyruvic oligophrenia have high blood levels of phenylalanine. The excretion of phenylpyruvic acid in the urine is probably an incidental phenomenon which may be related to the kidney's capacity to deaminate a certain portion of the excessive quantity of phenylalanine in the blood.

**Clinical Picture.** Patients are usually blue-eyed blonds with a tendency toward eczematous eruptions. The clinical picture is dominated by mental and nervous disorders including mental deficiency and extrapyramidal manifestations, such as rigid posture, muscular hypertonus, and exaggerated tendon reflexes.

**Diagnosis.** The mental deficiency and the excretion of large quantities of phenylpyruvic acid in the urine, 1 to 2 Gm. daily, are diagnostic. The latter condition may be demonstrated by the addition of ferric chloride to the urine, which, if it contains phenylpyruvic acid, turns dark green.

**Treatment.** No known therapy is of value. The total quantity of phenylpyruvic acid excreted in the urine and perhaps the blood level of phenylalanine may be reduced by substituting a diet low in protein and relatively high in carbohydrate and fat.

### HISTIDINURIA

Early in pregnancy there occurs an increased excretion of histidine in conjunction with the rise in urinary prolan titer. It has been shown that patients during pregnancy excrete a large proportion of ingested histidine. Histidine excretion is decreased immediately following parturition.

The presence of increased histidine in the urine has been suggested as a diagnostic aid or screening test in early pregnancy, although it is obviously not pathognomonic. It is probable that the increased renal excretion of histidine along with other amino acids is a reflection of the altered renal threshold in pregnancy. It is also possible that the metabolism of the imidazole groups in histidine, which presumably takes place in the liver by an enzyme (histidase), is impaired to some extent in pregnancy.

### TYROSINOSIS

Tyrosinosis is an abnormality in amino acid metabolism associated with the excretion of tyrosine and its breakdown products in the urine. The condition appears to be due to an inability to oxidize tyrosine beyond the keto acid stage. One case has been reported in medical literature (Medes, 1932). This patient excreted 1.6 Gm. of the keto acid. The feeding of phenylalanine to this patient resulted in increased excretion of tyrosine and its keto acid.

### FANCONI SYNDROME

This syndrome appears to be due to an inherited metabolic abnormality associated with the urinary excretion of excessive quantities of amino acids, glucose, and phosphorus.

**History.** Fanconi was the first to point to a renal tubular abnormality as the cause of rickets

associated with glycosuria in the case of a four-year-old girl whose clinical course and autopsy he described in detail in 1931. The familial incidence was noted and confirmed by others. In 1943 this rare disease was exhaustively reviewed by McCune *et al.*, who emphasized the normal glomerular function not found in renal rickets.

**Incidence.** The disorder is familial, and is carried as a simple recessive character.

**Etiology.** Fanconi believes that the amino-aciduria is associated with a generalized disturbance of deamination, both amino acids and amines being involved. Because it is the least soluble of the amino acids, cystine may be deposited in various organs of the body, and sometimes can be recognized by its crystalline structure in bone marrow biopsies.

The site of the disturbance in deamination is not known, but there is strong evidence that a metabolic defect exists in the proximal tubule of the kidney where it is assumed that glucose and phosphate are normally reabsorbed, the glucose presumably as the phosphate ester. The degree of glycosuria and amino-aciduria parallel each other. In at least one case of the syndrome a deficiency of phosphatase in the proximal convoluted tubule has been demonstrated. Experimentally, similar lesions may be produced in animals by long-continued alkalosis or by the excessive administration of the amino acid, serine. It has also recently been shown that a defect in the renal tubules is present, similar to that seen in renal acidosis (Milkman's disease), whereby the reabsorption of fixed base and bicarbonate in response to acidosis is impaired. This defect may bring about an excessive urinary loss of calcium which contributes to the skeletal demineralization.

**Pathology.** Aside from the demonstration of phosphatase deficiency in the proximal renal tubules, the pathologic changes are all secondary to protein and phosphate deficiency occasioned by the loss of essential amino acids in the urine. A weakened skeleton characterized by generalized osteoporosis and multiple fractures dominates the pathologic picture.

**Clinical Picture.** The fundamental aspects of the syndrome—i.e., increased amino acid, phosphate, and glucose excretion without hyperglycemia—usually cause no symptoms per se except that hypoglycemia may occur on prolonged fasting because of the virtual disappear-

ance of the renal threshold for glucose. However, the long-continued wastage of these substances results in demineralization of the skeleton, osteoporosis, and multiple fractures. The associated rickets is presumably due to deficiency of building blocks (phosphorus and amino acid) rather than to vitamin D deficiency. Hepatic insufficiency has been described as a cause of death. Sudden deaths have been reported following a glucose tolerance test.

**Treatment.** Most patients require orthopedic management. Marked improvement in fracture healing has been observed in a patient given 1 Gm. of disodium phosphate orally three times a day, 1 ml. of 10 per cent hydrochloric acid three times a day, and a high-calcium diet supplemented with 50,000 I.U. of vitamin D daily.

### HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)

**History.** The familial occurrence of cirrhosis of the liver in association with progressive cystic degeneration of the lenticular nuclei in the mid-brain was first described by Wilson in 1912 under the name *progressive lenticular degeneration*. Subsequently Hall demonstrated the identity of this condition with pseudosclerosis of the mid-brain (Westphal-Strumpell's disease) and proposed the term *hepatolenticular degeneration*. Fleischer, in 1912, pointed out the constant finding in both these conditions of a halo of golden brown pigmentation in Descemet's membrane at the limbus of the cornea.

**Incidence.** The disease, which is rare, appears to run in families, and its occurrence is favored by intermarriage among relatives. Ninety-six cases have been reported in 34 families. It appears oftenest between the ages of 10 and 25, and has been reported slightly more often in males than in females.

**Etiology.** The cause is unknown. Hereditary factors appear to play an important role. The liver disease usually precedes the cerebral changes, and dietary deficiencies have been suggested as the cause of both. The failure of the liver to detoxify some unknown neurotoxin has also been suggested. In one case tissue anoxia was implicated because of a peculiar inability of hemoglobin to release its bound oxygen in the peripheral tissues. This defect was corrected by the administration of cytochrome C.

Recently Uzman and Denny-Brown have found an excretion of excessive amounts of all the alpha amino acids in the urine of a patient with hepatolenticular degeneration occurring before there were any laboratory signs of liver insufficiency and at a time when a punch biopsy of the liver showed no increase of connective tissue in the portal areas. These authors raised the possibility that in hepatolenticular degeneration there may be a hereditary enzymatic defect in the metabolism of amino acids. Those "which can not be used by a defective enzymatic system are excreted by the kidney thus giving rise to a deficiency of amino acids essential for the maintenance of a functional and structural integrity of the liver and the basal ganglia of the brain."

**Pathology.** Grossly the liver appears shrunken and finely nodular. Microscopically there is a typical portal cirrhosis. In the brain, small cystic areas may be seen grossly in the putamen, globus pallidus, and adjacent structures; microscopically there is necrosis and loss of glial and nerve cells. Similar necrosis with softening may occur in the cerebral cortex. A characteristic finding is the presence of numerous neuroglial cells with large, pale nuclei, known as "Alzheimer cells, type 2."

**Clinical Picture.** Although the hepatic disease generally precedes the cerebral changes, the first symptoms are usually due to the latter. Gross tremor and athetoid movements appear early, followed by rigidity, postural changes, dysarthria, dysphagia, and psychotic symptoms. The pyramidal tracts are not involved. The liver and spleen are usually enlarged at some stage of the disease, but clinical and laboratory evidence of liver damage are not present until late. Death may result from portal obstruction with hemorrhage from ruptured esophageal varices, from intercurrent infection, or from aspiration pneumonia. Occasionally the symptoms may be due entirely to cirrhosis of the liver, and the cerebral lesions found only at autopsy.

**Diagnosis.** The diagnosis is made on the basis of the neurologic findings, a palpable liver and spleen, and the presence of the circumcorneal halo of golden brown pigmentation, the so-called Kayser-Fleischer ring, which is pathognomonic of the disease. A very few cases have been reported in which this finding was not present.

**Prognosis and Treatment.** The prognosis is invariably fatal, but the duration of the disease may vary from a few months to 40 years. Death

usually occurs within six years of the onset of symptoms.

Temporary improvement may be induced by the administration of a high-protein, high-calorie diet (over 4000 calories) similar to that employed in the modern treatment of cirrhosis of the liver. In the rare case showing an unusually high oxygen content of the venous blood, cytochrome C given intramuscularly in doses of 80 mg. daily may be of some value.

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### Nondiabetic Melituria

George W. Thorn and Kendall Emerson, Jr.

Definition
Physiology
Incidence
Classification
Glycosuric Melituria
True Renal Glycosuria
Pseudorenal Glycosuria
Alimentary Glycosuria
Transient Hyperglycemic Nondiabetic Glycosuria
Nonglycosuric Melituria
Pentosuria
Fructosuria
Galactosuria
Maltosuria
Sucrosuria
Lactosuria
Mannoheptulosuria
Summary
Conclusion

### DEFINITION

*Nondiabetic melituria* may be defined as an excessive quantity of sugar occurring in the urine in the absence of underlying diabetes mellitus.

### PHYSIOLOGY

Normally the renal tubules absorb all except traces of glucose filtered through the glomeruli. There is a maximum tubular reabsorptive capacity, however, even in the normal, which may be

exceeded by a large increase in the glucose filtered per unit of time through the glomeruli. In most instances the increased glucose level presented for tubular reabsorption is the result of an increased blood glucose concentration.

However, the so-called "renal threshold" is not defined by the blood glucose level alone, but rather reflects a relationship between the total quantity of glucose filtered per unit of time (glomerular filtrate concentration) and the tubular capacity to reabsorb glucose.

The disaccharides usually are not absorbed by the intestinal mucosa. The monosaccharides are absorbed and are converted to glycogen by the liver. Liver glycogenolysis leads only to glucose formation. Thus, the finding of fructose or galactose in the urine signifies excessive absorption of these sugars from the intestinal tract and/or inability of the liver to convert the monosaccharide to glycogen.

In *true renal glycosuria*, glucose is found in the urine at all times, even in the fasting state, and at all levels of blood sugar. In *pseudorenal glycosuria*, there is a temporary lowering of renal

threshold for glucose, and glucose may be found in the urine with blood sugars as low as 100 mg. Below this, however, and with hypoglycemia induced by insulin, glucose disappears from the urine. It is important to distinguish between *true* and *pseudorenal* glycosuria, since in the former diabetes rarely develops, whereas in the latter group the incidence of diabetes is actually higher than in the general population.

Glycosuria may be observed during the greater part of pregnancy; lactosuria occurs more commonly during the last days of pregnancy and lactation. Transient fructosuria may be observed following the ingestion of large quantities of fruit. It is to be distinguished, however, from the rare metabolic disturbance of idiopathic fructosuria.

### INCIDENCE

Transient nondiabetic glycosuria (*pseudorenal*) has been observed in 0.3 per cent of army inductees. *Nonglucose* melituria, other than lactosuria, is very rare. Among 29,000 patients with melituria, only nine patients with pentosuria and four with fructosuria were observed in the Joslin Clinic.

### CLASSIFICATION

Nondiabetic melituria may be classified conveniently as follows:

- I. Glycosuric Melituria:
  - A. True renal glycosuria
  - B. Pseudorenal glycosuria:
    1. Pregnancy
    2. Nephritis
  - C. Alimentary glycosuria
  - D. Transient hyperglycemic nondiabetic glycosuria
- II. Nonglycosuric Melituria:
  - A. Pentosuria
  - B. Fructosuria
  - C. Galactosuria
  - D. Maltosuria
  - E. Sucrosuria
  - F. Lactosuria
  - G. Mannoseuria

### GLYCOSURIC MELITURIA

#### TRUE RENAL GLYCOSURIA

Glycosuria which persists in the fasting state and with a blood sugar below 100 mg. per 100 ml.

is considered to be true renal glycosuria. The incidence is small, only 16 cases being observed among a group of 9000 patients with glycosuria. The condition is thought to be hereditary and familial, and, once developed, it persists throughout life. The importance of its recognition depends upon its harmlessness and the fact that patients with this disease almost never develop diabetes. The diagnosis of true renal diabetes can be established only if the following criteria are fulfilled:

1. Fasting blood sugar is within normal limits or lower than normal.
2. Glucose tolerance curve is normal or flat.
3. Glucose is present in every specimen, whether voided in the fasting state or after a meal.
4. Carbohydrate utilization is normal as indicated by a rise in respiratory quotient or a fall in serum inorganic phosphorus.
5. There is no disturbance in fat metabolism.

### PSEUDORENAL GLYCOSURIA

This condition is not uncommon. It is similar to true renal glycosuria with the exception that, as the blood glucose level diminishes toward 100 mg., the glycosuria diminishes and, under fasting circumstances, completely disappears. The glucose tolerance curve is normal; glucose utilization appears to be normal. There is an increased incidence of diabetes developing late in this syndrome, however, and it is therefore important to distinguish it from *true* renal glycosuria, in which glucose is *always* found in the urine and in which diabetes rarely develops.

During pregnancy there is lowered threshold for glucose, with the result that 10 to 15 per cent of normal pregnant women may show glycosuria. The usual explanation is increased blood volume, increased renal blood flow, and hence glycosuria at correspondingly lower blood sugar levels. It is probable that the mechanism is more complex than this, involving altered threshold for amino acids and other substances and perhaps being related to alteration in hormone secretion. The condition is benign and disappears after parturition.

Glycosuria may be observed at times in patients with nephritis and particularly in the early stage of bichloride nephrosis. Glycosuria under these circumstances results from impaired tubular absorption of glucose.

### ALIMENTARY GLYCOSURIA

This term is employed to designate the urinary excretion of glucose by certain apparently normal individuals after the ingestion of large quantities of cane sugar, glucose, or starch. Alimentary glycosuria is a condition in which the rate of intestinal absorption of glucose (normally 1.8 Gm. per kg. per hour) exceeds the body's ability to utilize glucose (approximately 0.8 Gm. per kg. per hour) and the capacity to store excess glucose as glycogen (presumably at least 1 Gm. per kg. per hour). Obviously, impairment of hepatic function will increase the incidence of alimentary glycosuria because of impaired glycogen storage; thyrotoxicosis, because of a greatly increased rate of absorption; amputation of extremities, because of greatly decreased muscle mass; gastrectomy and other gastrointestinal operations, because of altered rate of absorption. Alimentary glycosuria should be distinguished from the more frequent cases of postprandial glycuresis or increase in urinary reducing substances, most of which are nonglucose and which appear to be due largely to the excretion of unassimilable carbohydrates.

### TRANSIENT HYPERGLYCEMIC NONDIABETIC GLYCOSURIA

A variety of disturbances may cause temporary elevation of the blood sugar level above 150 mg. and hence, in the presence of normal or increased glomerular filtration rate, induce glycosuria. Although the mechanism in certain instances is similar to that associated with diabetes mellitus, it cannot be so classified because the status exists for relatively short periods only, being followed by normal glucose metabolism. In most instances a "stress" condition is present. Among the more frequent causes of transient hyperglycemic nondiabetic glycosuria are cerebrovascular accidents and brain injuries, particularly in the presence of increased intracranial pressure, acute coronary occlusion, thyrotoxicosis, and asphyxia. Pheochromocytoma, though rare, frequently is associated with glycosuria.

### NONGLYCOSURIC MELITURIA

#### PENTOSURIA

**Essential Pentosuria.** This disturbance is an inherited inborn error of metabolism, limited to Jews and more commonly observed in males.

Pentose is constantly present in the urine. It has no clinical significance.

**Alimentary Pentosuria.** Transient pentosuria may occur frequently in normal individuals following the ingestion of large quantities of fruits with a high pentose content—i.e., grapes, plums, cherries, and prunes. It is of no clinical significance.

**Diabetes Mellitus.** In certain patients with diabetes, pentosuria may occur on occasion and confuse the interpretation of diabetic regulation.

Pentose reduce metallic oxides in alkaline solution but is nonfermentable with yeast. Positive identification may be made by the following reactions: (1) formation of characteristic pentosazone crystals with phenylhydrazine; (2) gas production with *Escherichia coli* and *Salmonella paratyphi*, but no fermentation with *Candida tropicalis*; (3) reduction of Benedict's solution by pentoses in the cold.

### FRUCTOSURIA

Primary or idiopathic fructosuria is a rare inborn error of metabolism reported only so far in Jews. Approximately 50 cases have been described. It appears to be due to an inability on the part of the liver to convert fructose to glycogen. The origin of the fructose is dietary, and therefore there is usually no fructosuria under fasting conditions. The disturbance is benign.

Most instances of fructosuria are transient and are secondary to the ingestion of large quantities of fructose. Fructosuria is particularly likely to occur if there is liver damage which further impairs glycogen deposition. Fructosuria in combination with glycosuria may be observed in severe diabetes.

### GALACTOSURIA

Galactose tolerance is used as a test for hepatic disease and hyperthyroidism. In these two conditions the ingestion of galactose, in moderate quantities, is followed by a marked galactosuria. Large quantities must be ingested by normal persons to induce appreciable galactosuria.

A syndrome of "infantile galactosuria" has been described, which is occasionally observed among nursing infants. Following the ingestion of milk in sensitive children, hypergalactemia, galactosuria, proteinuria, mental disturbances, azotemia, anemia, and an enlarged liver and spleen have been reported. Replacement of milk

by a soybean formula has been observed to effect a complete cure. In this condition the livers of these infants were apparently unable to convert galactose to glycogen.

**Diagnosis.** Galactosuria is indicated by: (1) positive mucic acid test to exclude all reducing substances except lactose; and (2) positive phloroglucinol-hydrochloric acid reaction (Tollens) to exclude lactose.

### MALTOSURIA

This disorder has been reported, but the cases are not well documented. If it exists at all, it must be extremely rare.

### SUCROSURIA

This is a very rare abnormality in which sucrose apparently passes the intestinal barrier as such and is in part excreted in the urine. Obviously, it is most likely to occur after excessive ingestion of sucrose. Polyuria results, and the specific gravity of the urine is very high in sucrosuria. The urine fails to reduce Benedict's solution until it is hydrolyzed.

### LACTOSURIA

Lactosuria occurs in a considerable proportion of women during the period of lactation. It must be regarded as of no clinical importance. Lactosuria does occur during the last days of pregnancy.

**Diagnosis.** The following tests indicate lactosuria: (1) gas production with *Escherichia coli*, and no gas with *Salmonella paratyphi*; (2) positive mucic acid test and negative phloroglucinol-hydrochloric acid reaction (Tollens) to exclude galactose.

### MANNOHEPTULOSURIA

Mannoheptulosuria occurs in normal individuals after the ingestion of avocado.

### SUMMARY

The observation that urine contains substances capable of reducing Benedict's solution suggests glycosuria. Diabetes mellitus must be eliminated, as this is of utmost importance (see p. 613). The second step is to be certain that the reducing

substances are sugars (see section on Alkaptonuria in Chapter 86).

Diabetes mellitus or alimentary glycosuria should be considered if the urine contains a maximum quantity of reducing substance one hour after a glucose test meal. If the melituria persists with a normal blood sugar level, renal glycosuria should be suspected, particularly if glycosuria is present in urine specimens taken under fasting conditions. If glucose is present in the urine with an approximately normal blood sugar level, and if the glycosuria disappears on fasting, pseudorenal glycosuria (prediabetic) should be suspected.

Benedict's solution will be reduced at room temperature by urine which contains pentose, fructose, or mannoheptulose if the mixture is allowed to stand for a few hours. Baker's yeast will ferment glucose, fructose, galactose, and occasionally lactose, but not pentose.

### CONCLUSION

Every precaution should be taken to be certain one is not dealing with diabetes mellitus and to differentiate clearly between true renal glycosuria (a benign condition) and pseudorenal glycosuria (a potential diabetes).

Having performed the foregoing screening tests, the following qualitative tests may be performed to identify the reducing substance. Bial's orcinol test is positive only in the presence of pentose. Seliwanoff's resorcinol reagent gives a positive test for fructose, but unfortunately fructose reacts only slightly more rapidly in this reaction than does glucose. Tollens' phloroglucinol test is positive only in the presence of galactose. The mucic acid test is positive in the presence of either galactose or lactose. The osazones formed by either glucose or fructose are identical, but differ from the pentosazone. Polaroscopic study of the urine is now rarely performed in clinical laboratories.

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## Glycogenosis (von Gierke's Disease)

George W. Thorn and Kendall Emerson, Jr.

History  
Incidence  
Pathology  
Pathologic Physiology  
Clinical Picture  
Diagnosis  
Treatment

**History.** Von Gierke in 1929 described a condition characterized by enlargement of the liver and other organs with deposition in the cells of excessive amounts of glycogen. Although others had previously described clinical cases of this syndrome, they did not report that excessive glycogen was present.

**Incidence.** Less than 75 cases of this disease have been reported. The most common age group is that of infancy and early childhood. The disease appears to be congenital and possibly is transmitted as a Mendelian recessive characteristic.

**Pathology.** The organs most severely involved are the liver, heart, and kidneys. The liver is markedly enlarged, smooth, firm, and brownish in color. The liver cells, which are enlarged three times the normal size, are filled with glycogen. The heart may be tremendously enlarged and its myocardial fibers may be filled with glycogen. The kidneys may be increased to twice the normal size, with excess glycogen in the proximal tubules particularly. Characteristically, glycogen may be found in all of these organs long after death, suggesting a greatly impaired rate of glycogenolysis.

**Pathologic Physiology.** Glucose is converted to liver glycogen during and shortly after the ingestion of carbohydrate foods; in the fasting state, the liver glycogen is reconverted into glucose by a process known as glycogenolysis. In von Gierke's disease, liver glycogenolysis is markedly reduced. There is also some evidence that the conversion of glucose to glycogen is somewhat decreased. The cause of the impaired rate of hepatic glycogenolysis appears to be a deficiency of the enzymes or coenzymes necessary to convert glycogen to glucose. (Recent separation of a hyperglycemic factor from the pancreas suggested that unavailability of this factor may be

concerned. However, administration of this factor in one instance of von Gierke's disease produced no significant effect.) This has been documented by the following findings. Little or no elevation of blood glucose is observed following the injection of epinephrine, a fact providing further evidence of the immobility of the liver glycogen in this disease. In the fasting state, hypoglycemia develops readily because of decreased rate of glycogenolysis. The *brei* of normal livers is capable of hydrolyzing glycogen obtained from normal or glycogenotic livers; however, the *brei* from glycogenotic livers fails to hydrolyze any glycogen in either normal or glycogenotic livers. Post-mortem liver glycogenolysis, which is very active in the normal body, occurs most sluggishly in the organs of patients with glycogenosis. This abnormal stability is of fundamental importance.

Ketonemia, lipemia, and ketonuria are frequent in patients with glycogenosis because of the relative unavailability of glycogen stores, which places an increased demand on the mobilization and utilization of fat for energy requirements (see Chapter 59).

**Clinical Picture.** Two general types of the disease have been described—hepatorenal and cardiac. The patient with hepatorenal disease usually seeks medical aid because of a markedly distended abdomen and delayed growth and development. Subjective complaints are infrequent despite severe hypoglycemia. Occasionally epileptiform seizures or vomiting may occur. The child is usually pale and undersized, with a fat face and neck, but with thin buttocks. The abdomen is markedly distended with a huge liver. Ascites and splenomegaly are absent. Patients may live up to 20 years of age, but usually die earlier of intercurrent infections.

Patients with cardiac glycogenosis usually seek aid because of cyanosis, dyspnea, and edema. The heart usually is enlarged. Laboratory investigation reveals anemia, fasting hypoglycemia, ketonuria, and at times lipemia. The blood gly-

cogen level may be elevated. The blood glucose level fails to rise significantly after epinephrine injection. After glucose ingestion or intravenous glucose infusion, the fall in blood glucose level is slower than normal. This pseudodiabetic curve is due, no doubt, to impaired storage of glucose as glycogen rather than to a failure to utilize glucose normally in the periphery (see Chapter 59). Severe prolonged hypoglycemia may be induced by small doses of insulin. The liver function tests are usually normal.

**Diagnosis.** Diabetic hepatomegaly may be differentiated from glycogenosis by the presence of fasting hyperglycemia and glycosuria. Other

forms of congenital heart lesions, cardiac neoplasms, and beriberi heart disease should be considered in the differential diagnosis of cardiac glycogenosis.

**Treatment.** There is no specific therapy. Frequent feedings may decrease the ketosis and hypoglycemic episodes. Intercurrent infections should be treated promptly, since this is the most common cause of death.

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## Disorders of Pigment Metabolism

Kendall Emerson, Jr.

### Carotenemia and Carotenoderma

Definition

History

Incidence, Etiology, Diagnosis, and Treatment

Clinical Picture

### Melanosis and Melanuria

Definition

Metabolic Considerations

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### Ochronosis

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### Porphyrin Metabolism

History

Chemical Considerations

Congenital Porphyria

Treatment

Acute Porphyria

Chronic Porphyria

Secondary Porphyriuria

## CAROTENEMIA AND CAROTENODERMA

**Definition.** *Carotenemia* refers to the presence of an excessive amount of carotene in the blood. *Carotenoderma* signifies an excessive deposition of carotene in the skin.

**History.** Carotenemia was first described in the medical literature by Hess and Myers in 1919. It had been recognized prior to that time in Europe, where it was particularly prevalent during World War I.

**Incidence, Etiology, Diagnosis, and Treatment.** The incidence, etiology, diagnosis, and treatment of carotenemia have been discussed in Chapter 51.

**Clinical Picture.** Carotene is a normal constituent of the skin and contributes, along with other pigments, to its natural yellow color. When the level of carotene in the blood exceeds the range of 0.21 to 0.8 mg. %, the excessive deposition of carotene in the skin known as carotenoderma becomes clinically manifest. Carotene is in part excreted by the sebaceous glands and reabsorbed by the stratum corneum. Thus the canary yellow pigmentation is first noted in the nasolabial folds and over the forehead where sebaceous glands are numerous, and in the palms and soles where the stratum corneum is the thickest. The conjunctivas are not pigmented.

This condition is harmless and produces no symptoms by itself. It should direct attention to

its cause, which may be either an excessive dietary intake of carotene or failure of normal conversion of carotene to vitamin A as a result of liver damage.

### MELANOSIS AND MELANURIA

**Definition.** The deposition of an abnormal quantity of the pigment melanin is termed *melanosis*. This occurs most commonly in the skin but may be seen in other organs such as the colon (*melanosis coli*), the adrenal glands, and the nervous system. *Melanuria* signifies the excretion of melanin in the urine.

**Metabolic Considerations.** Melanin is formed by melanoblasts, which are specialized cells normally present in the basal layer of the epidermis at the junction of epidermis and derma. The exact chemical composition of melanin is unknown, but it is generally considered to be a polymer of tyrosine formed by the action of the enzyme tyrosinase. Melanin-producing cells contain an enzyme, dopa oxidase, which, in the presence of dihydroxyphenylalanine (dopa), produces a dark cytoplasmic color reaction. It has recently been shown that dopa oxidase and tyrosinase are the same enzyme acting first to oxidize tyrosine to dopa and then dopa to melanin. After the melanin has been formed, the pigment granules migrate to the cells of the epithelium where they are phagocytized. The melanin is eventually lost from the body largely through desquamation of the skin, and to a lesser extent through the intestinal tract, while none or only a very small amount is normally excreted

through the kidneys. This is not remarkable, since it is a large molecule and very slightly water-soluble.

The number and distribution of the melanin-producing cells of the body vary from one individual to another and are genetically determined. Frequently there is a congenital absence of these cells in various regions of the skin, resulting in splotchy areas of depigmentation known as *vitiligo*. Occasionally there is a total absence of melanoblasts in the skin, producing the condition termed *albinism*.

**Incidence and Etiology.** Melanosis may be caused by (1) an increased activity of a normal number of melanoblasts or (2) an increased number of melanoblasts. The vast majority of cases fall in the first category (table 86). Melanoblastic activity is stimulated by direct irritation of the skin as seen following exposure to ultraviolet rays, x-ray, and heat rays, or after prolonged irritation by mechanical, chemical, or infectious agents. A striking example of this is the pigmentation of vagabond's disease resulting from the chronic irritation of dirt, sweat, and vermin.

Vitamin deficiencies and local nutritional disturbances of the skin such as scleroderma may produce melanosis either by direct irritation or through interference with the normal metabolism of tyrosine. Thus, increased melanin pigmentation is seen in pellagra, in sprue, and, less often, in vitamin A deficiency (Darier's disease) and scurvy. The melanosis sometimes accompanying portal cirrhosis probably also has a nutritional basis.

Table 86  
CLASSIFICATION OF MELANIN PIGMENTATION OF THE SKIN\*

<i>Melanoblasts Normal in Number</i>		<i>Melanoblasts Increased in Number</i>
<i>External Causes</i>	<i>Internal Causes</i>	
Ultraviolet rays Roentgen rays Mechanical irritation Chemical irritation Vagabond's disease	Vitamin deficiencies Scleroderma Cirrhosis Blood dyscrasias Ingestion of arsenic Addison's disease Pregnancy Acanthosis nigricans Ochronosis	Freckles Pigmented nevus Neurofibromatosis Albright's syndrome Mucocutaneous melanosis with intestinal polyposis Neoplasms: Melanoma Melanotic epithelioma Melanotic carcinoma

\* S. W. Becker and M. E. Obermayer: "Modern Dermatology and Syphilology," Philadelphia, J. B. Lippincott Co., 1940.

Diffuse melanosis occurs in about 10 per cent of patients with Hodgkin's disease but is less commonly seen in the other blood dyscrasias. In these diseases it may be secondary to generalized pruritus with irritation from scratching, to malnutrition, or to x-ray or arsenic therapy. In chronic arsenic poisoning, melanosis occurs presumably as the result of a direct catalytic action of the metal on the normal pigmentary mechanism.

The pigmentation in Addison's disease represents a true melanosis. The cause of this is undetermined, but improvement following the use of vitamin C in some cases suggests a relationship in some manner to a deficiency of this vitamin. Such improvement following vitamin C therapy, however, is by no means the rule. It is noteworthy that, in adrenal insufficiency due to primary pituitary disease, pigmentation is conspicuous by its absence.

There appears to be some degree of control of melanin pigmentation by the gonadal hormones. The androgens tend to stimulate the melanoblasts generally, whereas the estrogens control the activity of certain specific melanoblastic cells such as those in the areolas of the breasts and in the vulva and perianal region, but at the same time inhibit the stimulating action of the androgens on the melanophores generally. Pigmentation of the skin is practically universal during pregnancy. Usually most of this pigmentation disappears following termination of pregnancy, but some remains about the nipples and the vulvar and anal regions. Marked pigmentation over the cheeks and forehead, known as *chloasma gravidarum*, may occur during pregnancy in individuals who are generously supplied with melanoblasts in these regions. This pigmentation usually disappears following pregnancy but sometimes persists to a greater or lesser degree.

*Acanthosis nigricans* constitutes a special form of melanosis in which increased melanin pigmentation is associated with hyperkeratosis and minute verrucous and papillomatous changes imparting a velvety feeling to the skin. The pigmentation usually begins and is most marked in the axillas, but may become generalized and involve the mucous membranes of the mouth. About half the cases are associated with abdominal cancer, although in a few instances the condition has been reported accompanying cancer of the breast and lung. In the remaining cases, acanthosis nig-

ricans is apparently a benign condition occurring primarily in children or at puberty and having an indefinite duration. Disturbances of hormonal function of the sex glands and vitamin deficiencies have been suggested as etiologic factors in this form of the disease. The microscopic picture of the skin is similar in both forms of the disease and is diagnostic.

Melanin deposits are occasionally seen in the colon, associated with intestinal obstruction or severe constipation in heavily pigmented individuals, particularly Negroes (*melanosis coli*). A rare familial condition characterized by the syndrome of spotty melanin pigmentation of the skin about the mouth and nose and on the buccal mucous membranes, hands, and fingers, in association with extensive small-intestinal polyposis, has recently been identified as a clinical entity.

Except for freckles and pigmented nevi, melanosis associated with an increased number of melanoblasts is a rare condition. In neurofibromatosis (von Recklinghausen's disease), sharply outlined brown blotches, *café au lait* spots, may develop and suggest the diagnosis. This pigmentation is considered to be due to a localized anatomic abnormality in the cutaneous nerves controlling the melanoblasts. A similar patchy skin pigmentation is seen in polyostotic fibrous dysplasia (Albright's syndrome) localized to the same dermal segments in which the bone lesions of osteitis fibrosa cystica are found. This condition occurs in children and is accompanied by precocious puberty, especially in the female. A rare condition characterized by the association of skin melanomatosis with melanomatosis of the central nervous system has been described and is considered to be a congenital neurocutaneous syndrome similar to the pigmented spot occasionally seen over the site of a spina bifida occulta.

Melanotic carcinomas usually arise from a pigmented nevus, but may occur in a nonpigmented mole or callus or in normal skin. These malignancies may produce a diffuse melanin pigmentation of the skin in addition to the pigmentation of direct metastases.

Melanuria occurs only in those cases of melanotic carcinoma with extensive primary or metastatic growths. It is seen very rarely in patients with Addison's disease and in heavily pigmented individuals with obstipation or chronic intestinal obstruction, and may be detected chemically following intense solar irradiation. At autopsy it

may be detected in these conditions by silver stain, as a granular deposit in the cells of the renal tubules as well as in the reticuloendothelial cells of the liver, spleen, and lymph nodes. Its presence in the urine is indicated by a brown-black color. In some cases a colorless breakdown product of melanin, pyrocatechol, may be excreted which turns yellow on addition of ferric chloride. The dark urine occurring in porphyriuria, alkapturia, and hemoglobinuria has occasionally been mistakenly reported as melanuria, and should be carefully distinguished.

Ochronosis is another form of melanosis due to excessive melanoblastic activity; it is described below.

**Symptomatology.** The symptomatology of melanosis is that of the underlying disease which causes it. Its appearance varies widely, according to hereditary characteristics and etiologic factors. The pigmentary color may vary from light brownish yellow to blue-black, depending on the amount of pigment formed. It may be diffuse, covering the entire body, or localized to exposed or irritated surfaces, to skin folds, or to mucous membranes. It may occur in irregular splotches of any size or in sharply demarcated spots such as in freckles and pigmented nevi.

**Differential Diagnosis.** Melanosis should be differentiated from pigmentation due to the absorption of metals, such as argyria, chrysiasis, and bismuthia, by the history, by the color and location of the pigment deposits, and by biopsy. Hemochromatosis, hemosiderosis, xanthomatosis, and carotenoderma may be distinguished by similar means.

**Treatment.** Melanosis in itself is a harmless condition and requires no treatment. It should be considered an important diagnostic sign of an underlying disease toward which treatment should be directed.

## OCHRONOSIS

Ochronosis is a rare metabolic pigmentary disorder, characterized by increased deposition of pigment in bone, cartilage, ligaments, and skin.

**Incidence.** It is a rare disorder, less than 100 cases having been reported. Ochronosis is more frequent in men than in women.

**Etiology.** Increased pigment deposition characteristic of ochronosis may occur under three widely varying circumstances:

1. In association with an inborn error in the metabolism of tyrosine and phenylalanine with resulting excretion of homogentisic acid. It is not unusual for several members of the same family to be affected (see Alkaptonuria, p. 708).

2. Following prolonged external use of carbolic acid preparations.

3. In association with disturbed melanin metabolism.

**Pathology.** Excessive deposition of extracellular pigmentation in cartilage, bone, tendons, and other fibrous tissues throughout the body characterizes the condition of ochronosis. The cartilaginous structures may be so heavily pigmented as to be coal black in color. In its chronic form there is an increased tendency for degenerative changes such as arteriosclerosis and osteoarthropathies to take place, with resulting impairment in function.

**Clinical Picture.** Ochronosis may be asymptomatic. Early manifestations include bluish or bluish black discoloration of the cartilages, particularly those of the ears and nose, and pigmentation of sclera, cornea, and skin of the face. Transillumination may reveal increased density of bones, particularly of the hands. One may observe greenish brown axillary sebum and brownish black cerumen. Characteristically, the urine turns from brown to black on standing or upon addition of alkali. The disease runs a chronic course, later being characterized by progressive development of degenerative changes, especially involving the larger joints, with premature systemic arteriosclerosis.

**Diagnosis.** The diagnosis is frequently first suggested by the observation of a brown discoloration of the linen stained by urine. In addition, the urine will turn from brown to black upon standing or upon addition of alkali. Later an observation of bluish black discoloration of the cartilages makes the diagnosis quite evident.

**Treatment.** Obviously, carbolic acid preparations should be discontinued if they are being used. If homogentisic acid is demonstrated (alkaptonuria), vitamin C in large doses (500 mg. daily) and a diet of restricted protein, high carbohydrate, and fat may be used; the latter may be helpful if the ochronosis is associated with melanuria. In long-standing cases, therapy will be of little avail except for those measures directed toward correcting or relieving the degenerative changes.

## PORPHYRIN METABOLISM

**History.** Hans Fischer, in 1915, first described, named, and isolated in crystalline form the uroporphyrins and coproporphyrins studied in the famous case of congenital porphyria (Petry). MacMunn, Sallet, and Garrod were the first to recognize the presence of porphyrins in normal urine. Since then much progress has been made in our understanding of the origin and significance of these substances, but a great deal still remains to be learned.

**Chemical Considerations.** The porphyrins are pigments possessing a basic structure of four pyrrole rings linked by methine bridges. These pigments occur throughout the plant and animal worlds. The individual porphyrins differ from each other according to the nature of the eight possible side chains. In addition, each individual porphyrin has a number of stereoisomers. In the plant world actinoporphyrin is the basic pigment of chlorophyll. The porphyrin of blood pigment is protoporphyrin. The porphyrins are also components of vital enzyme systems such as the cytochromes.

There are two other porphyrins of clinical significance—i.e., coproporphyrin and uroporphyrin. Although their names suggest that one is found in feces and the other in urine, both may be found in either feces or urine, and normally they are probably derived from ingested plant and animal tissues; there is no evidence to indicate that they are derived from hemoglobin breakdown. Two isomers of each of these por-

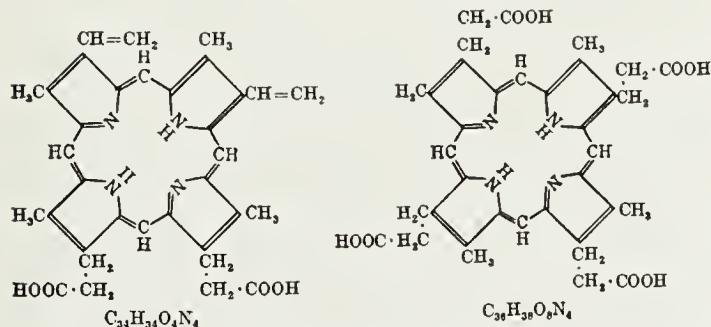


FIG. 139. Structural formulas of coproporphyrin I and of protoporphyrin 9 (isomer type III), according to H. Fischer. (Courtesy, Watson and Larson: *Physiol. Rev.*, 27:478, 1947.)

phyrins are found naturally—types I and III (fig. 139). The liver appears to be the most important organ of excretion. Normally 10 to 100 micrograms of coproporphyrin are excreted in the urine and 150 to 300 micrograms in the feces

per 24 hours, type I predominating over type III in a ratio of four to one. In certain pathologic conditions the quantity of these porphyrins excreted in the urine and feces may be greatly increased, and the ratio of type I to type III may be reversed.

Ordinary quantities of uroporphyrin and coproporphyrin in the urine do not affect its color, nor are they detectable by usual means. When they occur in pathologic quantities, the color of the urine may vary from Burgundy red to almost black. On occasion coproporphyrin may be excreted in the urine as porphobilinogen, a colorless compound which on exposure to sunlight is changed to coproporphyrin. It is possible to detect porphobilinogen rather easily by the use of Watson's modification of the Ehrlich reaction. A pink fluorescence may be detected if urine containing porphyrin is exposed to filtered ultraviolet rays. More detailed analysis may be made by use of the characteristic absorption bands for the alkaline porphyrin. The type I and III isomers can be separated only by chemical fractionation and melting point analysis.

**Congenital Porphyria.** Congenital porphyria is a very rare disease first described by Gunther in 1911. It represents an inborn error of metabolism in which there may be a persistence of fetal pyrrole metabolism. It is inherited as a recessive Mendelian characteristic and is more common in males.

The disease begins, as a rule, early in life, although tardive types have been described. It is characterized by: (1) the continuous excretion of large quantities of uroporphyrin and coproporphyrin, type I, in the urine; (2) increased amounts of porphyrin in the blood; (3) pigmentary discoloration of teeth, bones, and skin; and (4) cutaneous eruption—light sensitivity.

The color of the urine varies from pink to red to black, depending upon the concentration of porphyrins and their state of oxidation. It may deepen in color on standing if the urine is kept acid; oxidation and color development are prevented by alkalinity. The pink to brown disoloration of the enamel of the teeth is characteristic. Occasionally the bones of the hand are pigmented sufficiently to be demonstrable by transillumination. The skin is sensitive to ultraviolet light, and the lesions vary from erythema to vesicle formation and large bullae (hydroa aestivale, urticaria solaris). These occur most

commonly over the face, neck, and hands, and with healing there is scarring and hyperpigmentation. Other features include hirsutism and, later in life, hepatomegaly and splenomegaly. It should be noted that many cases of photosensitivity are not associated with porphyrinuria.

**Treatment.** Exposure to sunlight should be avoided, and the skin lesions should be protected from secondary infection. Liver extract and large doses of vitamins have been reported to decrease the porphyrin excretion.

**Acute Porphyria.** Acute porphyria is a rare metabolic disorder which occurs more commonly in women than in men. It may be familial; it appears to be inherited as a Mendelian dominant characteristic. The mortality rate is high.

The disease becomes manifest during the second to fifth decades and is characterized by: (1) intermittent excretion of large quantities of uroporphyrin and coproporphyrin, type III, in the urine; less often type I predominates; (2) acute colicky lower abdominal pain; (3) neurologic manifestations.

The urine is usually dark brown or Port wine colored; it contains large quantities usually of the type III isomers of both uroporphyrin and coproporphyrin, the former usually in the form of the zinc complex. There is usually increased porphobilinogen which may be detected on oxidation.

The acute attack includes abdominal pain and spasm without localizing signs, *but with leukocytosis*. The abdominal symptoms may be easily mistaken for manifestations of renal colic, acute appendicitis, cholelithiasis, or pancreatitis. Occasionally jaundice may be present. Acute porphyria should always be considered among the causes of an acute abdominal crisis.

The nervous manifestations which almost invariably accompany the attack include neuritic pains extending down the legs, and occasionally foot drop or wrist drop. Rarely, ascending paralysis with death from respiratory failure may occur. There may be disorientation and transient hypertension. One of the acute attacks is likely to prove fatal. Patients with acute porphyria do not exhibit the light sensitivity characteristic of the congenital type. In patients who recover, the porphyrinuria usually disappears in the course of three to four weeks.

**TREATMENT.** It is stated that the acute symptoms may be ameliorated by the intravenous ad-

ministration of calcium. The use of barbiturates and other drugs which are known to be associated with porphyrinuria in susceptible patients should be avoided.

**Chronic Porphyria.** In certain instances the disease runs a protracted course. It is not possible to classify these cases as either typically congenital or acute porphyrias. There may be light sensitivity; there is a continuously increased urinary excretion of porphyrin; abdominal symptoms such as cramps, nausea, and vomiting dominate the clinical picture; and nervous depression frequently occurs. Under this heading may be included idiopathic porphyrinuria in which the continued urinary excretion of excessive amounts of type III coproporphyrin is associated with no symptoms whatsoever. Either chronic or acute porphyria may follow the prolonged use of barbiturates, sulfonmethane, sulfonethylmethane, sulfonamides, and numerous other drugs. It is believed that this effect of drugs occurs principally in those individuals already having a latent inherited tendency to porphyrinuria.

**Secondary Porphyrinuria.** In certain pathologic processes the quantity of porphyrin excreted may be greatly increased and the ratio of type I to type III reversed. Examples of this are lead poisoning and other heavy metal intoxications, some cases of pellagra, the anemias, infections, and liver disturbances. Regarding the latter, increased urinary excretion of type I coproporphyrin has been observed in hepatitis, mechanical jaundice, and cirrhosis. In hepatitis the porphyrinuria may persist long after apparent recovery. In chronic alcoholism there may be increased excretion of type III coproporphyrin which is usually restored to normal when alcohol is withheld, unless cirrhosis of the liver is present.

Excessive urinary excretion of type I coproporphyrin occurs frequently in acute febrile states such as pneumonia, lung abscesses, and rheumatic fever. The finding of an excessive urinary excretion of type III coproporphyrin in acute anterior poliomyelitis has led to an investigation of the presence of porphyrins in nervous tissue which is still in progress. In a significant proportion of cases of Hodgkin's disease the urinary excretion of either type of coproporphyrin may be increased.

In all of these disorders the increased porphyrinuria is an accompaniment of the underlying disease, the symptomatology of which deter-

Table 87  
PORPHYRINURIAS

<i>Classification</i>	<i>Predominant Coproporphyrin Type</i>	<i>Fecal Coproporphyrin Excretion</i>	<i>Symptoms</i>
Congenital . . . . .	I	Increased	Pigmentation Light sensitivity Dark urine
Acute . . . . .	III or I	Increased	Abdominal pain Neurologic manifestations Leukocytosis
Chronic . . . . .	III and I	Increased	Either those of congenital or those of acute
Idiopathic . . . . .	III		No symptoms
Secondary			
Hepatitis . . . . .	I	Decreased	Those of primary disease
Biliary cirrhosis and obstruction . . . . .	I	Decreased	
Alcoholic cirrhosis . . . . .	III	Decreased	
Pernicious anemia . . . . .	I	Increased	
Aplastic anemia . . . . .	III	Increased	
Hodgkin's disease . . . . .	III or I	?	
Acute poliomyelitis . . . . .	III	?	
Other febrile states . . . . .	I	?	
Heavy metals . . . . .	III	Increased	
Drugs . . . . .	III	Increased	
Normal Values ( $\mu$ g. per day)	Urine I 14-90 III 1-35	Feces I 150-300 III 0	

mines the presenting clinical picture. It is not known whether the abnormality in porphyrin metabolism contributes significantly to the clinical picture.

**DIFFERENTIAL DIAGNOSIS.** The usual method of detection has been by measurement of the fluorescent light having a maximum wave length of 6250 angstroms produced by an exciting ultraviolet ray of approximately 4000 angstroms. The final diagnosis of porphyrinuria depends upon the identification of the characteristic spectral absorption bands of alkaline porphyrin at 6220, 5760, 5390, and 5040 angstroms. The commonest substances which may be mistaken for porphyrin in the urine are urorosein, indican, hemoglobin, bilirubin, and, rarely, melanin. These may be identified relatively simply by the proper chemical means.

**TREATMENT.** Secondary porphyria is merely a harmless manifestation of an underlying disease toward which treatment should be directed.

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## Methemoglobinemia and Sulfhemoglobinemia

George W. Thorn and Kendall Emerson, Jr.

Methemoglobinemia  
Clinical Picture  
Sulfhemoglobinemia  
Clinical Picture

### METHEMOGLOBINEMIA

Although cases of cyanosis following drug ingestion and cases of congenital cyanosis which undoubtedly represented congenital methemoglobinemia were described in 1844, van den Bergh was the first to differentiate clinically these abnormal pigments by spectroscopic means in 1905.

Methemoglobin is an oxidation product of hemoglobin which is unable to function as an oxygen carrier. It is easily reduced again to active hemoglobin, however, and in the normal red corpuscle there is a reconversion mechanism which keeps the ratio of hemoglobin to methemoglobin at about 99 to 1. Small amounts of methemoglobin produce cyanosis, and, with large amounts, symptoms of hypoxia result. Methemoglobin is usually found within the erythrocyte. Certain drugs, however, may produce both intracellular methemoglobin and methemoglobin in the serum. Methemoglobin may be identified by its band of light absorption at 630 millimicrons, which disappears on the addition of potassium cyanide. This serves to distinguish it from sulfhemoglobin, and from methemalbumin, a pigment found only in the serum.

**Clinical Picture.** There are several types of intracellular methemoglobinemia to be distinguished clinically. *Congenital idiopathic methemoglobinemia* is due to a defect in the red corpuscle mechanism which ordinarily reverts methemoglobin to hemoglobin. Patients with this disorder maintain a level of about 40 per cent methemoglobin, but show very few symptoms. Cyanosis is present from birth, and there is usually a secondary polycythemia. Idiopathic methemoglobinemia may be treated successfully with either ascorbic acid (100 to 200 mg. per day) or methylene blue given orally in enteric coated capsules (200 to 300 mg. per day).

*Drug-induced methemoglobinemia* is a much

more common variety of the disorder. The most frequent causative agents are nitrates, aniline derivatives including acetophenetidin and acetanilid. Nitrates taken orally may be converted into nitrites in the intestinal tract and hence produce methemoglobinemia. This conversion is particularly likely to occur in infancy and in patients with ulcerative lesions of the gastrointestinal tract. (Methemoglobinemia has been observed in children with poisoning due to wax crayons. Nitrate poisoning from well water is a potential hazard of babies born in rural areas and put on formulas calling for water.) Aniline derivatives are dangerous because of their ability to pass through the intact skin. These drugs not only may produce methemoglobinemia but also may result in an appreciable degree of red corpuscle destruction. Ascorbic acid is ineffective in counteracting methemoglobinemia associated with the above medicaments; whereas methylene blue, given in doses of 1 to 2 mg. per kg. intravenously or 5 mg. per kg. orally, is usually effective. The apparent ineffectiveness of methylene blue in certain instances may be due either to the presence of other abnormal pigments in the blood or to the presence of such large amounts of drug as to counterbalance the effect of methylene blue.

"*Enterogenous methemoglobinemia*," so-called, occurs in patients with gastrointestinal disorders, particularly with ulcerative lesions of the bowel and diarrhea. These patients may experience attacks of cyanosis, palpitation, severe headache, and occasionally syncope. It is thought that nitrites produced by intestinal bacteria are absorbed and produce methemoglobin. Rare cases of acquired hemolytic anemia accompanied by bouts of methemoglobinemia have also been observed.

### SULFHEMOGLOBINEMIA

Segler, in 1863, first discovered the pigment sulfhemoglobin, produced by the action of sulfurated hydrogen on the blood. Later the clinical

differentiation of abnormal pigments was made by van den Bergh.

Sulfhemoglobin is an abnormal pigment found within the red corpuscle, capable of producing intense cyanosis. Although the exact structure is not known, it is likely that a sulfur molecule is introduced into the pyrrole ring. Once formed, sulfhemoglobin remains in circulation until the red corpuscles containing it are destroyed. It shows a band of absorption in the spectrum at 618 millimicrons which does not change after the addition of potassium cyanide, but which disappears after the addition of hydrogen peroxide.

**Clinical Picture.** Sulfhemoglobin may be produced by the same drugs which cause methemoglobinemia. In addition, however, the patient

must either receive a sulfur-containing medication or be constipated. *Enterogenous sulfhemoglobinemia* is reported more frequently in the literature than enterogenous methemoglobinemia. The symptoms are the same, but the cyanosis, instead of clearing over a few hours, disappears gradually over a period of three or four months. There is no treatment other than to stop the causative drug or to improve the bowel habits of those patients in whom constipation is the precipitating factor.

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## Lipoidosis and Xanthomatosis

George W. Thorn and Kendall Emerson, Jr.

Definition  
History  
Etiology  
Pathology  
Clinical Picture  
Primary Essential Xanthomatosis  
Secondary Xanthomatosis  
Primary Essential Lipoidoses

### DEFINITION

*Lipoidosis* is a general term applied to a group of diseases characterized by an abnormal accumulation of lipids in various body tissues (Thannhauser). The term *xanthomatosis* is restricted to the specific forms of lipoidoses in which abnormalities in cholesterol metabolism are involved. This latter form of lipoidosis is by far the most important clinically.

### HISTORY

Addison and Gull presented the first clear-cut description of xanthomatosis in 1851. Since then, additional clinical entities have been described by Gaucher, Niemann, Pick, Tay, Sachs, and others. To Klenk, however, belongs much of the

credit for the identification of the types of lipids involved in the various syndromes.

### ETIOLOGY

From the standpoint of etiology the lipoidoses may be divided into a primary group in which the exact cause is unknown, and a secondary group in which the abnormal accumulation of lipids is a consequence of a generalized disturbance in fat metabolism, with or without hyperlipemia, such as may occur in diabetes, arteriosclerosis, nephritis, and hypothyroidism.

*Primary or essential lipoidoses* may be subdivided into one group in which the serum lipids are abnormal in quantity or quality, and a second group in which the disturbance is limited to an abnormal accumulation of lipids intracellularly, the serum lipids being normal. When the serum lipids are elevated or when abnormal types of lipids are present in the circulating blood, the abnormal intracellular accumulation of lipids is probably a result of phagocytosis and storage of the excess or abnormal fat in the reticuloendo-

thelial system. When the serum lipids are normal, on the other hand, the increase in intracellular lipids must be presumed to be the result of a local cellular abnormality involving either an increased synthesis or a decreased utilization of fat by the particular cells involved. In all forms of primary lipoidosis there is a marked familial tendency. Although the disorder may appear at any age, it is most often acquired congenitally and becomes manifest clinically during infancy or early childhood.

### PATHOLOGY

The characteristic pathologic picture common to all the lipoidoses described above is the accumulation of masses of large cells containing fat droplets, the so-called "foam cells." These cells stain with various fat stains, depending on the type of lipid involved, and may cause a surrounding low-grade inflammatory reaction with secondary infiltration of lymphocytes, macrophages, and eosinophils. In some instances the inflammatory reaction may be so marked as to obscure the foam cells and present a picture of a specific granulomatous lesion. Disturbance of function of various organs may result from pressure or replacement by aggregations of foam cells. Accumulations of foam cells may occur anywhere in the body, but their localization is largely determined by the particular defect of lipid metabolism involved.

The pathologic picture of secondary xanthomatosis differs somewhat from the primary disease in that the inflammatory reaction is usually less pronounced, the cells involved are for the most part components of the reticuloendothelial system, and there may be extracellular deposits of cholesterol.

### CLINICAL PICTURE

#### PRIMARY ESSENTIAL XANTHOMATOSIS

**Hypercholesteremic Type.** This condition includes the xanthoma tuberosum and xanthoma planum of the skin described by Addison and Gull, and xanthelasma of the eyelids. In addition, plaque-like and nodular accumulations of cholesterol-laden cells may occur in tendon, liver and bile ducts, endocardium, and walls of blood vessels. The level of both total and esterified cholesterol is elevated in the serum, the ratio

remaining normal except in the presence of liver damage. The concentration of serum lecithin and total fatty acids usually is moderately increased.

The clinical course and prognosis of this disease are usually benign. In rare cases, however, death may occur from involvement of the coronary arteries, or from obstructing xanthomas of the biliary system producing so-called xanthomatous biliary cirrhosis. Restriction of cholesterol in the diet is definitely of benefit in lowering the serum cholesterol level, but apparently has no effect on xanthoma already present.

**Normocholesteremic Type.** In this type of xanthomatosis the lesions may be found in the skin, bones (chiefly the skull and pelvis), brain and medulla, dura, lungs, pleura, lymph nodes, liver, and spleen. Included in this group are xanthoma disseminata of skin, eosinophilic granuloma of bone, and Hand-Schüller-Christian disease.

The characteristic skin lesion, xanthoma disseminata, occurs as a mahogany-colored papular eruption most commonly in the axillas, antecubital fossae, and on the sides of the neck. Eosinophilic granuloma of bone is now generally considered a late manifestation of osseous xanthomatosis wherein most of the foam cells have been replaced by low-grade inflammatory tissue.

The Hand-Schüller-Christian syndrome is a clinical entity characterized by bony defects in the membranous bones, exophthalmos, and diabetes insipidus. The bony defects occur most commonly in the skull and represent replacement of membranous bone by xanthoma cells and granulomatous tissue. This same type of tissue also invades the orbit, producing exophthalmos, and the tuber cinereum and the pituitary stalk, resulting in diabetes insipidus (see p. 566). Frequently the anterior pituitary is also involved, as evidenced clinically by retarded growth and the appearance of the adiposogenital syndrome in children.

Xanthomatous lesions of the skin, lymph nodes, liver, spleen, and lungs may occur as part of the picture of the Hand-Schüller-Christian syndrome or as separate and isolated phenomena.

Essential xanthomatosis of the normocholesteremic type may regress spontaneously, with recovery, provided local organ damage has not been too extensive. Roentgen therapy has been shown to be remarkably effective, particularly in causing disappearance of the bone lesions.

## SECONDARY XANTHOMATOSIS

Any disease associated with an increased level of neutral lipid in the serum may cause both intracellular and extracellular deposition of cholesterol, chiefly in the skin and reticuloendothelial system. This deposition differs from primary xanthomatosis in that it varies directly with the level of the serum lipids and may disappear entirely if the neutral fat in the blood is lowered to normal by restriction of dietary fat. The skin manifestations are termed eruptive xanthomatosis because they may appear and disappear rapidly. Secondary xanthomatosis is seen in inadequately controlled diabetes, hypothyroidism, and less commonly in chronic pancreatitis. The possible acceleration of arteriosclerotic degenerative changes must be considered in all cases of hypercholesterolemic lipoidosis or xanthomatosis. Localized xanthoma formation may occur in association with chronic inflammatory processes, particularly in organs rich in fat, such as the breast and mesentery (Whipple's disease).

## PRIMARY ESSENTIAL LIPOIDOSES

This group includes three known clinical entities in which there is an intracellular accumulation of fat other than cholesterol—namely, Gaucher's disease, Niemann-Pick disease, and Tay-Sachs disease.

**Gaucher's Disease.** First described by Gaucher in 1882, this is a familial disease characterized by the deposition of a cerebroside, kerasin, in the cells of the reticuloendothelial system. There is evidence that an abnormal type of kerasin, containing glucose instead of galactose, is formed in this condition. Apparently this substance cannot be utilized and is therefore picked up and stored by the reticuloendothelial system as a foreign body. Traces of cerebroside, not a normal constituent of blood, have been found in the serum of patients with this disease.

The clinical features of Gaucher's disease are marked hepatosplenomegaly and progressive anemia, the result of infiltration of the liver, spleen, bone marrow, and lymphatic system with large, pale, polygonal cells filled with cerebroside. If the onset is in infancy, the disease is usually fatal within six months. The later in life it becomes manifest, the longer the duration. Death eventually occurs from anemia or intercurrent infection. No effective treatment is known, although splenectomy is indicated if hypersplenism, as evidenced by neutropenia, platelet deficiency, or anemia, is present, or in cases in which a greatly enlarged spleen must be removed for mechanical reasons.

**Niemann-Pick Disease.** This disease is a congenital familial disorder of lipid metabolism in which sphingomyelin accumulates in the histiocytes and reticulocytes of all organs, including the glial cells of the brain. Clinically it is characterized by hepatosplenomegaly, diffuse pigmentation of the skin and mucous membranes, Mongoloid facies, mental deterioration, and cachexia terminating fatally in the first two years of life. The brain in patients with this disease contains less than the usual proportion of cerebrosides.

**Tay-Sachs Disease.** Pathologically and clinically this disease resembles closely Niemann-Pick disease. It is frequently associated with familial amaurotic idiocy, in which case it may be recognized by the cherry red macula. In this condition, however, the accumulations of cells contain a galactoside which is a normal constituent of brain tissue but apparently abnormally metabolized. The sphingomyelin content of the brain is markedly reduced.

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# Part V

## DISORDERS DUE TO CHEMICAL AND PHYSICAL AGENTS

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## Section 1—Chemical Agents

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# The Intoxications

Marshall Clinton

Introduction
General Principles
Phenol Intoxication
Alcoholism
Methyl Alcohol (Methanol) Intoxication
Benzene Poisoning
Carbon Tetrachloride Poisoning
Cyanide Intoxication
Barbiturate Intoxication
Carbon Monoxide Intoxication
Intoxication by Morphine and Related Alkaloids
Metal Poisoning
Bromide Poisoning

### INTRODUCTION

Nearly all chemical agents can be toxic under certain conditions. Chemical substances which, when introduced into the body in relatively small quantity, are capable of producing serious injury to health or death to individuals in average health are considered to be poisons. It is evident that many chemical agents, including many if not most of our therapeutic drugs, fit this definition.

The physician is primarily concerned with the recognition and treatment of poisonings; the detection and identification of the particular poison involved depends on the specialist in toxicology. Since the practicing physician is the first individual to encounter such cases, however, he must be alert to recognize their possible nature, and to take the proper steps to secure samples which will permit the toxicologist to carry out the identification of the toxic agent involved.

### GENERAL PRINCIPLES

Poisoning may be accidental or intentional. Accidental poisonings most commonly occur in the home as a result of the ingestion of toxic chemical agents, especially in children, who are prone to convey any article to the mouth. Accidental poisoning may also result from the inhalation of toxic dusts, gases, or vapors. This may occur in the home, but more commonly

arises in the course of an individual's employment. Intentional poisonings may result from self-indulgence in a drug, or may be directly suicidal or criminal in origin.

In general, chemical poisons have the greatest effect on those tissues which they encounter in the highest concentration. It is not possible, however, to predict the site of action of organic poisons, such as most of the commonly used drugs. This is especially true of the alkaloids and other complex substances. Irritant substances, on the other hand, usually have their greatest action on the organs concerned with their absorption: notably the stomach, small bowel, and liver in the case of ingested substances, and the upper respiratory tract and lungs in the case of inhaled substances. Metallic poisons are prone to affect the organs responsible for their excretion, notably the kidneys and colon.

Chemical agents which have an acute toxic action generally affect the gastrointestinal tract, kidney, and liver; those with chronic toxic actions may also damage these organs, and, in addition, may affect the hemopoietic system or the central nervous system. The musculoskeletal system, including the heart muscle, may be affected, but this is seldom clinically evident.

The diagnosis of chemical intoxication is difficult. Many of the intoxications may mimic other more common disease states. They are encountered relatively infrequently, and therefore the possibility of poisoning is not considered in many instances. There are certain characteristic signs, however, which should arouse suspicion that one is dealing with a chemical intoxication. The possibility of some type of poisoning should be considered in any patient who is comatose or stuporous, especially if there is no fever, or if there are no localizing neurologic signs and no abnormal findings in the urine, blood, or spinal

fluid on routine examination. Chronic intoxication, with selective damage to various tissues or organ systems, may be even more difficult to recognize. The poisoning may develop insidiously over a long period of time. As local irritation of the skin, gastrointestinal tract, or respiratory system may be entirely absent, the relationship between exposure and effect may be completely overlooked, unless one is familiar with the clinical picture produced by a myriad of potentially toxic agents.

The importance of an adequate and accurate history cannot be overemphasized. Particular attention should be paid to the occupation of the patient. It is not sufficient to know this in general terms. One must learn exactly what the individual does in his occupation, and to what substances he is exposed in the course of his work. Since most poisonings will occur away from work, however, one must also pay particular attention to the social activities and home habits of the individual. It is also necessary to learn something of his behavior patterns and emotional reactions, particularly if deliberate ingestion or inhalation of a toxic agent is suspected. It need hardly be emphasized that such history frequently can be better elicited from others than from the patient.

The role of the toxicologist in identifying drugs and poisons has already been mentioned. His work may be greatly simplified and expedited if the clinician will supply the proper samples for analysis. The importance of saving any vomitus and urine cannot be overemphasized. It can be discarded later if not needed, but, once discarded, it is gone forever. Blood should be drawn and reserved for subsequent study, as many substances are present in the blood in considerable concentration during the acute phase of a poisoning, but disappear from the blood stream as recovery ensues.

The treatment of the chemical intoxications will, of course, depend on the particular agent involved. While it is not possible to generalize the subject of treatment, there are certain principles which deserve emphasis. Acute poisonings constitute real medical emergencies, and prompt action may be lifesaving. The first effort in any poisoning should be directed at terminating the absorption of the injurious agent.

If the poisoning is a result of ingestion, the stomach should be emptied, preferably by lav-

age, as the action of emetics may be uncertain in the presence of nervous system depression. Lavage, to be effective, must be repeated and thorough. A large-caliber tube should be used, as the usual Levin or Rehfuss tube is so easily plugged. After the stomach has been emptied (save the recovered material!) it is desirable to instill a saturated solution of magnesium sulfate or some other saline cathartic into the stomach in order to promote rapid emptying of the intestinal tract and to inhibit further absorption of the toxic agent. The use of a saline cathartic is especially desirable if the poison is known to be water-soluble. If it is known to be a fat-soluble substance, it may be desirable to use mineral oil instead of a saline cathartic, as the agent will dissolve in the oil and be lost with it; but, in case of doubt, the saline cathartic is preferred.

If the poisoning is due to a toxic gas or vapor, the affected individual should be transferred to an area where the atmosphere is not contaminated, and kept warm and at complete rest. If natural breathing is interrupted, artificial respiration should be started *at once*, as the chances of recovery following cessation of respiration are inversely proportional to the elapsed time before artificial respiration is started. If artificial respiration is begun within four minutes of the time breathing ceases, the victim has a fair chance of recovery. If the delay extends to 10 or 12 minutes, recovery is most unlikely. If the gas or fume has a direct action on the lungs, complete rest is essential, and pure oxygen should be administered. If the gas or vapor has no local effect, but exerts a systemic action, elimination can be greatly accelerated by the administration of *oxygen containing 7 per cent carbon dioxide*.

When the individual has been immersed in, or a considerable area of skin or clothing has been contaminated with, an agent known to exert a serious local or systemic action, the immediate removal of the contaminating material from the skin and the discarding of the clothing are essential. In such an instance speed is imperative. Clothing should be cut away, and the skin should be cleansed by copious flooding with cool water and *gentle* wiping. Agents other than water may be more desirable for removing certain substances, but water is useful in any case because of its general availability. Substances not readily soluble in water are removed to a large extent by the direct mechanical action of the water.

Finally, one should consider the use of stimulants in any poisoning associated with nervous system depression. Nikethamide ("Coramine"), amphetamine, or caffeine may be of distinct benefit. Hot coffee may be of help when other agents are unavailable, provided the individual is able to swallow. Otherwise, its use may lead to aspiration. Coffee enemas, however, are of no benefit. Conversely, the intravenous use of a short-acting, rapidly oxidized barbiturate anesthetic (usually "Pentothal sodium") in the occasional cases associated with central nervous system stimulation and convulsions may be life-saving. Care should be taken, however, not to complicate a given intoxication with superimposed barbiturate poisoning.

### PHENOL INTOXICATION

Phenol (carbolic acid) is a white, crystalline solid which has a characteristic odor. It is highly hygroscopic, and is usually encountered in aqueous solution. It is a general protoplasmic poison, and is one of the oldest antiseptics known. Phenol is widely used in industry, is commonly encountered in the laboratory, and is used in dilute solution as a household antiseptic as well as in hospitals. It is frequently incorporated into ointments or lotions applied to the skin as a means of controlling itching. This sometimes leads to poisoning.

**Incidence.** Poisoning by phenol and related substances (such as the phenol-cresol mixtures in substances such as "Lysol") not infrequently follows the accidental or suicidal ingestion of their solutions. Also, such accidental or deliberate ingestion may result in death or serious burns of the mucous membranes of the mouth and esophagus, with subsequent scarring and stricture of the esophagus. Occasional fatal cases have been reported following extensive exposure to phenolic solutions as a result of spillage.

**Toxicology.** Phenol is a powerful and corrosive contact poison, which acts upon, and is also absorbed rapidly through, the intact skin. It is a general protoplasmic poison which acts on tissue by denaturing and coagulating the proteins. Concentrated solutions of phenol produce severe burns of both skin and mucous membrane surfaces, leading to extensive local necrosis in a relatively short time. Phenol is especially dangerous and insidious because it exerts a local anesthetic action which may prevent the perception

of painful stimuli until serious burns have been sustained. Phenol is readily absorbed through the skin or mucous membranes, but is not sufficiently volatile at ordinary temperatures to permit the absorption of toxic quantities via the respiratory tract.

Phenol not only produces severe burns, characterized by the presence of dry, white eschars which later turn yellowish brown and which heal slowly with extensive scarring, but also produces serious systemic poisoning following absorption from the skin or mucous membranes. Systemic poisoning by phenol may occur following exposure of the skin to relatively dilute aqueous solutions of phenol which do not produce serious local reactions. The extent of absorption of phenol from the skin appears to be determined primarily, if not entirely, by the area exposed, and not by the concentration of the solution. The absorption of phenol is extremely rapid. Phenol is detoxified rapidly, primarily in the liver. It is excreted rapidly in the urine, mostly after combination with organic acid or oxidation, but to a limited extent as free phenol. Small amounts may leave the body via the respiratory tract, producing inflammation there.

Exposure of large areas of skin to either dilute or concentrated phenol will lead to serious systemic poisoning in addition to the local effects. Extensive exposure may be followed by loss of consciousness and death within an hour, due to respiratory paralysis. Less extensive exposure may produce headache, faintness, vertigo, mental confusion, and even delirium. There may be marked pallor and dyspnea. Vomiting and/or convulsions sometimes occur. Death from shock may occur. Extensive exposure may result in an acute hemorrhagic nephritis, and the urine is usually dark and strongly acid. The dark urine may be one of the chief indications of the possibility of phenol or cresol poisoning.

**Symptoms.** The general effects of phenol on the body are primarily a result of its action on the nervous system. It affects nerve tissue in general and the vital medullary centers in particular. Phenol exerts an analgesic effect initially, but this may progress rapidly to marked depression of the medullary centers for control of circulation and respiration, with lowering of blood pressure, rapid, feeble pulse, and slow, shallow breathing. The occurrence of absorption in motor areas of the brain probably accounts

for the convulsions which may be encountered, as these usually occur early prior to the onset of unconsciousness.

Repeated exposure of the skin to dilute solutions of phenol may lead to local changes characterized by the development of a reddish, maculopapular dermatitis, by paresthesia or anesthesia, and, finally, by alterations in skin texture and color. In addition, serious systemic changes may take place. Digestive disturbances characterized by loss of appetite, vomiting, difficulty in swallowing, increased salivation, and diarrhea are frequent. Headache, vertigo, fainting, and mental disturbances also occur. Urinary changes suggestive of nephritis may be encountered. In addition, there may be melanotic discoloration of various tissues, especially cartilage, involving the external ears, the face, and even the hands.

**Treatment.** Contamination of the skin or clothing with phenol constitutes a serious emergency which requires *immediate* attention. The slightest delay may be fatal. If the skin and/or clothing are contaminated with phenol, *all* involved clothing should be removed *at once*, and the phenol removed from the skin by copious flooding with warm water or by washing with 25 to 70 per cent alcohol. Glycerin may also be used to remove phenol, but mineral oil should be avoided because it will dissolve phenol to a limited extent only. Various strengths of alcohol are advocated by different authors for removing phenol. In general, the stronger solutions are more effective and smaller volumes are required. However, the use of strong alcohol solutions over large areas of body surface may be accompanied by sufficient absorption of alcohol to augment the already present effects from phenol; therefore, caution in their use is necessary, as alcohol also depresses the nervous system, adding to the depression already resulting from phenol.

Phenol which enters the eye should be removed by protracted flushing with water, followed by the application of a bland oil. Alcohol should not be used in the eyes.

Prompt removal of contaminated clothing and cleansing of the skin should be supplemented by indicated general supportive measures, such as the use of respiratory stimulants such as oxygen and 5 to 7 per cent carbon dioxide, artificial respiration if necessary, intravenous fluids, and rest and warmth. Epinephrine should be used with caution because of the possibility of in-

ducing ventricular fibrillation, but nikethamide ("Coramine") or caffeine and sodium benzoate may be given with impunity.

### ALCOHOLISM

Alcoholism may be defined as the clinical state induced by the ingestion of relatively large amounts of alcoholic beverages. Both acute and chronic forms of alcoholism are recognized. The cost to mankind of the pain, sudden death, physical deterioration, and moral disintegration produced by alcohol is immense. Few individuals escape being touched by alcoholism either by personal experience or by contact with alcoholic relatives or close friends at some period of their lifetime; yet the use of alcohol continues to be socially acceptable. Five to 50 per cent of fatal automobile accidents are due to alcohol, and up to 25 per cent of psychiatric patients have some alcoholic background. Adequate facilities for the treatment of alcoholics and education of the public to the hazard of alcoholism are woefully inadequate, although commendable progress in the establishment of a sane approach to the problem, such as the establishment of treatment centers, has been noted since World War II. The key to the problem appears to be education and understanding; certainly punishment or prohibition have been ineffective so far.

**Toxicology.** Alcohol is rapidly absorbed via the gastrointestinal tract and/or the lungs, the former being the usual route of entry. Alcohol is absorbed from the stomach and small bowel, the rate of absorption varying directly with the concentration imbibed and inversely with the food content of the stomach. About 50 per cent of a drink of alcohol is absorbed in the first 15 minutes; absorption is 99 per cent complete in three hours. Alcohol is distributed to all tissues of the body in direct proportion to their water content, the concentration being highest in the blood (and urine), a third lower in the tissues, and lowest in bone and lipoid tissues. Otherwise, it is fairly evenly distributed in all tissues, including the brain. Very little alcohol is excreted; 90 to 98 per cent is oxidized to carbon dioxide and water. The rate of oxidation of alcohol is fairly constant at about 10 ml. per hour; approximately 7 calories are liberated for each gram of alcohol burned. Alcohol is a "false food"; it can replace carbohydrate and fat as a source of energy, but its excessive use may result in exclusion of ade-

quate amounts of protein and vitamins from the diet.

The most important clinical effects of alcohol are exerted on the central nervous system. Alcohol is a nervous system depressant in all concentrations; the apparent stimulating effect of small doses is a result of depression of the highest cortical centers with consequent release of their inhibiting action on lower centers. When enough alcohol is absorbed, the veneer of adult civilized behavior is removed; the baser animal instincts are released—as all who have attended a social cocktail party are aware.

There is a definite relation between the alcohol content of the blood or tissues and the clinical state of the individual. Blood concentrations below 0.05 per cent indicate that the individual is definitely sober; levels of 0.05 to 0.15 per cent are tolerated by some but are associated with signs of clinical intoxication in others. Concentrations above 0.15 per cent are usually considered as being proof of being "under the influence"; levels of 0.2 to 0.4 per cent correspond to obvious drunkenness; and levels of 0.5 to 0.8 per cent result in coma which is likely to be fatal.

**Acute Alcoholism.** Acute alcoholism may be defined as the clinical state induced by the intake of sufficient alcohol to poison the central nervous system, resulting in a temporary disordering of faculties which renders the individual incapable of carrying out his normal activities, thereby making him dangerous to himself and to others. The symptoms depend on the amount of alcohol consumed and the surroundings of the individual at the time. Small or moderate amounts produce a sense of well-being and warmth. Inhibitions are lost, and the tongue is loosened. Judgment and coördination are impaired, although the euphoria which supervenes results in an inward feeling of great superiority. Larger amounts result in thickened speech, muscular incoördination, numbness of the extremities, and later slurring of speech and blurring of vision. The skin is flushed as a result of peripheral dilatation. Heat loss is accelerated, and may become serious to individuals exposed to the elements. The outward response may be one of either aggression or withdrawal, with either euphoria or a depressed, sad mood, depending on the personality of the individual and the circumstances attending his intoxication. Sufficient alcohol will erase this variation in response; the narcotic stage is

eventually reached. It is characterized by a complete loss of inhibitions, with a behavior pattern of loquaciousness, excitement, abusiveness, or sullenness. The eyes fail to coördinate, muscular performance is impaired, the memory is lost or confused, and the speech is thickened and slurred. This state progresses to loss of consciousness and sensory perception, as well as to muscle tremors. The terminal and fatal stage of acute alcoholic intoxication is characterized by medullary depression with slowing of respiration, loss of temperature control, circulatory collapse, abolition of reflexes, and death. Alcoholic intoxication of less severe degree may lead to a condition of automatic behavior (alcoholic automatism) which is not remembered upon recovery.

The acute alcoholic episode is generally followed by a period of severe headache and gastrointestinal disturbances. In addition, pneumonia may result from exposure or aspiration of vomitus during coma. Finally, criminal acts or sexual promiscuity may result from the release of abnormal personality traits and loss of judgment accompanying the acute alcoholic episode.

**DIAGNOSIS.** The diagnosis of acute alcoholic intoxication is usually not difficult, owing to the characteristic odor of the breath and the behavior pattern. It must be remembered, however, that the presence of an alcoholic breath on a comatose individual does not eliminate the possibility of a head injury, cerebrovascular accident, subarachnoid hemorrhage, diabetic or uremic coma, or poisoning by other depressant drugs. The common error is the failure to examine carefully individuals admitted in coma with an alcoholic odor to the breath—especially those brought in by the police. Any comatose individual must be examined carefully and completely.

**TREATMENT.** Recovery will be spontaneous in most instances. It can be made less unpleasant by the administration of analgesics and amphetamine sulfate. If alcoholic coma is present, however, considerable care may be necessary. The stomach should be lavaged, as it may contain enough unabsorbed alcohol to cause death if absorbed in a reasonable time. If the temperature is subnormal, adequate warmth must be maintained. The administration of oxygen containing 5 to 10 per cent carbon dioxide to stimulate respiration is desirable. Cerebral stimulants (amphetamine, "Coramine," or caffeine and

sodium benzoate) are of considerable benefit. The intravenous injection of 100 ml. of 50 per cent glucose and 20 units of regular insulin will accelerate recovery. Thiamine hydrochloride should also be given (100 to 200 mg. daily), as many alcoholics have thiamine deficiencies.

**Chronic Alcoholism.** Chronic alcoholism represents the clinical state resulting from the frequent or steady ingestion of moderate amounts of alcohol or from repeated bouts of drunkenness. In the broad sense, any individual who is unable to resist alcohol is a chronic alcoholic; the boundary between the social drinker and the chronic alcoholic is nebulous. The chronic alcoholic is an inadequate, insecure, or psychopathic individual; alcohol represents an escape from unpleasant reality which cannot be resisted. The chronic alcoholic is fundamentally a psychiatric problem, but is also a medical problem because of the disorders of organic function which are encountered. Most of these represent deficiencies in nutrition; others, nervous system changes induced by alcohol; and a few, the effects of other toxic agents which are ingested along with the alcohol.

**TOXICOLOGY.** The acute episodes of intoxication experienced by the chronic alcoholic are similar to those of acute alcoholism, except for a greater ability to conceal the drunken state. Certain other changes are characteristic of the chronic alcoholic.

The gastrointestinal tract of the chronic alcoholic exhibits progressive change, characterized by loss of appetite, gastric distress, nausea and vomiting, irregular bowel function, and a desire for highly spiced foods. These changes are due to bowel irritation by alcohol, vitamin deficiencies, and nervous irritability. The beer drinker may have an atonic dilated stomach, as a result of repeated overdistention.

Degenerative changes are encountered in other organs. Fatty infiltrations in liver and kidneys are frequent. Dilatation of skin vessels, particularly of the nose (acne rosacea), is common. Cirrhosis of the liver is definitely associated with chronic alcoholism, although the exact role of excessive alcohol intake and the accompanying nutritional deficiencies is not entirely clear. Nervous system changes, both peripheral and central, are prominent. These may be organic or functional, irreversible or reversible. Tremor of the hands and tongue occur early. Peripheral neuritis de-

velops later, as a result of thiamine or related deficiency, but is common.

**MENTAL MANIFESTATIONS.** The mental manifestations of chronic alcoholism are most interesting. It must be emphasized, however, that many of the mental aberrations of the chronic alcoholic induce rather than follow the chronic alcoholic state. Nervousness and emotional instability are common. Rage and remorse may follow in rapid succession. Judgment is impaired and initiative is blocked.

Certain clinical syndromes related to chronic alcoholism are particularly important, although their exact relation to the condition is not entirely clear. The following clinical disturbances are of importance:

1. **DELIRIUM TREMENS.** Delirium tremens is an acute and temporary psychotic episode encountered in chronic alcoholics, usually following withdrawal of alcohol or after exceptionally heavy drinking bouts. It does not follow acute intoxication of normal individuals. It is characterized by excessive motor activity, disorientation as to time and place, and vivid visual and auditory hallucinations. The visual hallucinations are usually terrifying, and involve the presence of small hostile creatures such as bats, ants, snakes, rats, and so forth. Paranoid thoughts and muttering speech are frequent. Muscular tremor and activity are increased. The episode usually lasts from 3 to 10 days, ending in recovery; but death from exhaustion or accompanying infection may occur. The episode should be handled with adequate but carefully controlled sedation (chloral hydrate, barbiturates, or paraldehyde), maintenance of adequate fluid intake and electrolyte balance, and administration of glucose, insulin, and vitamins (particularly thiamine and nicotinamide). Further alcohol administration should be avoided.

2. **ALCOHOLIC HALLUCINOSIS.** This may be acute or chronic. The individual remains well oriented and maintains a clear sensorium, but is aware of auditory hallucinations, which may be decidedly disturbing. Paranoid reactions, especially jealousy, suspicion, and distrust, are common.

3. **KORSAKOFF'S PSYCHOSIS.** This psychosis occurs in long-standing alcoholism, and is characterized by loss of memory and presence of confabulation (filling in of imagined details to cover up the memory loss). The onset may be sudden with a severe psychotic episode, or gradual with a progres-

sive deterioration of memory. The condition is associated with evidences of B vitamin deficiency (polyneuritis and pellagrous skin changes). The prognosis is poor; intensive vitamin therapy is of little value.

4. ACUTE ALCOHOLIC EXCITEMENT. Certain individuals react to an alcoholic debauch with an acute, brief psychotic episode characterized by excitement, combativeness, and sometimes hallucinations. Recovery is spontaneous.

5. ALCOHOLIC DETERIORATION. The moral fiber of the chronic alcoholic may deteriorate, leaving an irresponsible, dissolute, and carefree individual who is prone to violate the social and moral codes on the slightest impulse.

DIAGNOSIS. The diagnosis of chronic alcoholism is not difficult if an adequate history can be obtained. The chronic alcoholic may be suffering from other conditions, however, such as general paresis; these patients must all be studied carefully. If an alcoholic history is not obtained the diagnosis may be difficult; but the presence of acne rosacea, coarse tremor of hands and face, liver enlargement, avitaminoses, emotional instability, and mental deterioration should arouse suspicion. Psychiatric evaluation is a decided aid in such cases.

TREATMENT. The treatment of chronic alcoholism is generally unsatisfactory. Psychotherapy is essential if any permanent results are to be obtained, as the underlying personality defect responsible for the development of the disorder must be remedied. The individual must be made aware that he is in need of help, and a positive attitude of coöperation developed. Organizations such as "Alcoholics Anonymous" will undertake this task with zeal, and can be of great benefit. Any program of treatment must include not only the correction of any existing nutritional deficiencies, but also the establishment of a positive pattern of thought and interest to replace the void remaining after alcohol is withdrawn. Complete abstinence from drink is essential if relapse is to be avoided.

A new approach to the treatment of alcoholism has recently been achieved as a result of the introduction of tetraethylthiuram disulfide ("Antabuse"). "Antabuse" may be taken for weeks or months in doses of 0.25 to 1 Gm. without producing any symptoms. If any alcoholic beverage is ingested during the period of "Antabuse" administration, then a series of extremely unpleasant

symptoms develop which are generally sufficiently severe to preclude further intake of alcohol. The principal symptoms encountered when a person maintained on "Antabuse" takes an alcoholic drink are vasodilatation, pounding headache, nausea, and intense discomfort; unconsciousness may occur. The symptoms are generally believed to be due to the accumulation of aldehydes in the blood as a result of a blocking of the route of oxidation of alcohol. "Antabuse" may be effective in restraining the alcoholic from drinking, through fear of the unpleasant sequelae, but the underlying psychic disturbance responsible for the alcoholism is not altered by its use. "Antabuse" may become a useful adjunct to psychotherapy, but at present it must be considered an extremely interesting, possibly useful, somewhat dangerous substance.

The use of emetic drugs to produce a conditioned reflex with vomiting after alcohol consumption, and revulsion at the mere thought of a drink, has been advocated repeatedly; the results have been disappointing in most hands. Whether or not "Antabuse" will be more effective remains to be determined.

### METHYL ALCOHOL (METHANOL) INTOXICATION

Toxicology. Methyl alcohol (wood alcohol, methanol,  $\text{CH}_3\text{OH}$ ) may cause serious intoxication leading to blindness or death. Methyl alcohol is a commonly used industrial solvent, and poisoning may arise from inhalation of its fumes or ingestion of beverages adulterated with it. Accidental poisonings are especially prone to occur under circumstances which prevent access to alcoholic beverages and lead to the drinking of methyl alcohol as a substitute. Methyl alcohol produces central nervous system depression quite similar to that of ethyl alcohol, and in addition may produce severe acidosis and damage to the optic nerve which may lead to temporary or permanent blindness. Hyperglycemia is often found. The effects of a single dose of methyl alcohol will persist for several days, as it is only slowly oxidized in the body to formaldehyde and formic acid. There is a wide variation in susceptibility to optic nerve damage from methyl alcohol. Blindness may follow the ingestion of as little as 10 ml., whereas the lethal dose is approximately 100 to 250 ml.

**Symptoms.** The symptoms of methyl alcohol poisoning are rather similar to those of the acute alcoholic spree, except that the inebriation which occurs persists for a long period, and may be accompanied by marked weakness, headache, photophobia, and blurring of vision. Blindness may occur in a few hours or after several days.

**Diagnosis.** The diagnosis of methyl alcohol poisoning may be difficult when no history of ingestion of methyl alcohol is obtainable. It should be suspected in the presence of severe mental depression, confusion, delirium, or coma accompanied by an odor of methyl alcohol on the breath, labored and rapid respiration, blurring or loss of vision, dilated and sluggish pupils, haziness of the disk margins, and hyperemia of the retina. The urine is strongly acid due to the presence of formic acid, while methyl alcohol may be demonstrated in the blood.

**Treatment.** The treatment of methyl alcohol poisoning should be directed at removal of any methyl alcohol remaining in the gastrointestinal tract, maintenance of adequate fluid balance and nutrition, correction of the systemic acidosis, and prevention of circulatory or respiratory collapse. Gastric lavage should be performed at once, and a saline cathartic left in the stomach to empty the intestinal tract. Intravenous fluids containing sodium bicarbonate or  $\frac{1}{6}$  M sodium lactate should be given in liberal quantity. Thiamine, nicotinamide, and vitamin K should also be given. Pain, restlessness, or delirium can be relieved by the use of opiates, scopolamine, or barbiturates in usual dosage. If respiratory depression or circulatory collapse is present, oxygen or oxygen-carbon dioxide mixtures should be administered. Caffeine and sodium benzoate, ephedrine, amphetamine, or "Coramine" may also be of benefit.

## BENZENE POISONING

Benzene ( $C_6H_6$ ) may produce serious or fatal poisoning. Acute benzene poisoning is typical of the effects produced by most highly volatile hydrocarbons encountered in high concentration. Benzene may in addition produce serious, even fatal, delayed poisoning following repeated exposure to very low concentrations which may escape sensory detection. Benzene is cheap, and is an excellent solvent. It has been used extensively in the rubber, paint, and printing industries, and may be present in motor fuels. Fortu-

nately, the hazards it presents are now well known, and its use curtailed or controlled by statute. Unfortunately, however, occasional cases of benzene poisoning continue to occur.

**Etiology:** ACUTE BENZENE POISONING generally results from the inhalation of relatively high concentrations of the vapor. Exposure to air containing benzene in concentrations of 19,000 to 20,000 parts of benzene per 1,000,000 parts of air (61 to 65 mg. per liter of air) causes death within a few minutes. Mild symptoms supervene following exposure to 1500 to 3000 parts per 1,000,000 parts of air (5 to 10 mg. per liter) for a period of several hours. The drinking of benzene produces symptoms similar to those following inhalation of like amounts of the substance, plus local evidences of acute irritation of the mouth, throat, esophagus, and stomach.

CHRONIC BENZENE POISONING results from repeated or continuous exposure to relatively low concentrations of benzene vapor. The level and degree of exposure necessary to produce poisoning apparently vary widely. There are at least two well-authenticated cases of poisoning by repeated exposures to only 75 parts per million; yet many chemists repeatedly expose themselves to far higher concentrations over periods of many years with no apparent ill effects.

The American Standards Association and most states have set an arbitrary limit of 100 parts per million as the maximum permissible benzene concentration for workers exposed to this substance during an eight-hour day. Massachusetts and Oregon have set limits of 75 parts per million, whereas New York considers 50 parts per million as the highest permissible level. Inasmuch as the body develops no tolerance to benzene, it is generally considered that the only absolutely safe concentration for benzene is zero. The inadequacy of a limit of 100 parts per million is indicated by well-authenticated reports of at least two cases of benzene poisoning following exposure to only 75 parts per million. Skin contact may also lead to chronic benzene poisoning, as benzene can be absorbed through the intact skin.

**Toxicology:** ACUTE BENZENE POISONING results from its depressant action on the central nervous system following absorption. In addition to its general narcotic action, benzene apparently has a characteristic neuroirritant effect, which accounts for the hypertonicity, excitement, and convulsions which are encountered. Benzene also

sensitizes the heart muscle to the action of epinephrine, so that instant death due to ventricular fibrillation may occur. Muscular activity increases the rapidity of onset and the severity of acute benzene poisoning. Persons dying of acute benzene poisoning generally show absence of blood clotting, and widespread petechial hemorrhages in the brain, pleura, pericardium, urinary tract, intestinal tract, mucous membranes, and skin.

Recovery from acute benzene poisoning requires from one to four weeks. Shortly after exposure there are temporary symptoms of chest and head pain, shortness of breath, giddiness, nausea, and loss of appetite. These symptoms may persist for two or three weeks, whereas cardiac distress and a peculiar yellow pallor of the skin may last for as long as a month.

**CHRONIC BENZENE POISONING** is more frequent, more insidious, and usually more serious than acute benzene poisoning. Practically all of the chronic effects of exposure are a result of the influence of benzene or its oxidation products on the blood-forming system. A variety of reactions may be encountered, and there is little correlation between the degree and duration of exposure and the severity or nature of the findings in the blood on microscopic examination. There is no single change in the blood-forming organs which is universally present in benzene poisoning. The bone marrow may be hypoplastic, fairly normal in appearance, or hyperplastic. Abnormal forms of young cells may abound, and reasonably well-documented instances of the development of leukemia as a result of chronic benzene exposure have been cited. Cases with symptoms fairly soon after exposure usually have fewer cells in the bone marrow, whereas cases developing later are more apt to have an increased number of cells in the marrow. It is probable that this represents an early weeding out of those who develop hypoplastic changes, rather than a gradual shift from one type of response to the other.

The findings on microscopic examination of the blood are as variable as the bone marrow response. They may consist of a reduction in red corpuscle, white cell, or platelet levels, in any two of these, or in all three. These changes can develop gradually or suddenly. The blood usually shows a moderate reduction in red corpuscles (below 3,500,000), white cells (below 4500), and platelets.

**Symptoms:** **ACUTE BENZENE POISONING.** Acute exposure to benzene produces rapidly increasing symptoms of tightening of leg muscles, dizziness, excitation, and pallor, followed by weakness, headache, flushing, breathlessness, apprehension of death, and constriction in the chest. Visual disturbances, tremors, and muscular weakness also occur. Consciousness may be lost, or acute mania and delirium may develop. Convulsions are fairly frequent. Death may be rapid or may be delayed for several hours to several days following exposure.

**CHRONIC BENZENE POISONING.** The early symptoms of chronic benzene poisoning are extremely vague and varied. There may be anorexia and weight loss, followed by abdominal pain, nausea, and vomiting. Dyspnea may be severe, and convulsions are occasionally encountered. There may be kidney involvement, evidenced by the presence of albumin, casts, and blood. Later the symptoms are those associated with the severe refractory anemia or thrombocytopenia with bleeding tendency which occurs. The characteristic finding is the presence of a refractory anemia.

**Diagnosis.** The diagnosis of benzene poisoning must depend on a history of exposure. There are no diagnostic criteria which distinguish chronic benzene poisoning from aplastic anemia or agranulocytosis due to other causes. Determination of the ratio of organic to inorganic sulfates in the urine may be of value in estimating the degree of exposure, but is of little or no diagnostic aid.

Examination of the blood for evidences of benzene poisoning should never be limited to a single determination such as a red corpuscle or white cell count, but should consist of a complete study of the red, white, and platelet fractions. Progressive changes are of more significance than any absolute alteration.

**Treatment:** **ACUTE BENZENE POISONING** should be considered as an acute emergency. The victim must be removed from the contaminated atmosphere at once, and kept at *complete* rest subsequently. Care must be taken that the rescuers are not also overcome by the fumes. Frequently, rescuers who exert themselves will subsequently die, whereas the inactive victim recovers. Artificial respiration should be administered if natural breathing has been interrupted, and oxygen may be administered.

**CHRONIC BENZENE POISONING** is extremely re-

fractory to treatment. Practically all therapeutic measures have failed, although transfusions are at least temporarily useful in combating severe anemia. The administration of fairly large doses of ascorbic acid (100 mg. per day) may be of value, as may the use of liver extract. General supportive measures should, of course, be carried out.

Prophylaxis is most important. Working conditions should be safeguarded, either by the use of less toxic materials or by adequate ventilation. Workers should be selected carefully and re-examined periodically, particular attention being paid to the blood picture. Any deviations from previous levels should be considered as sufficient reason for removal from exposure.

### CARBON TETRACHLORIDE POISONING

Carbon tetrachloride ( $\text{CCl}_4$ ) is an occasional source of serious, sometimes fatal poisoning. Carbon tetrachloride is a nonflammable and practically incombustible, clear, colorless liquid with a slightly sweetish odor suggestive of chloroform. It is a cheap, commonly used household and industrial solvent and is the usual filling ingredient of the "squirt gun" type of fire extinguishers. Carbon tetrachloride is generally considered to be entirely safe because of the absence of any fire hazard; actually, it is far more toxic than most of the organic solvents which present a fire hazard.

**Etiology.** Carbon tetrachloride poisoning may follow the ingestion or inhalation of this agent. Most cases of carbon tetrachloride poisoning result from the inhalation of the vapor and its absorption from the lungs. This may occur when it is used as a home cleaner or when it is used as an industrial solvent or cleansing agent with inadequate ventilation. Occasional cases occur when carbon tetrachloride is ingested accidentally or following its administration as a vermifuge.

Symptoms have been reported following exposure to as little as 35 to 45 parts of carbon tetrachloride per million parts of air, and exposure to concentrations of 60 to 70 parts of carbon tetrachloride per million parts of air may produce nausea, vomiting, and headache. The maximum allowable concentration of carbon tetrachloride for persons exposed during an eight-hour day has been set at 50 parts per million parts of air by

Massachusetts and Oregon, at 75 parts per million by New York, and at 100 parts per million by most other states.

**Toxicology.** Carbon tetrachloride has a double toxic action on the body. Moderately heavy exposures produce an immediate narcotic effect characterized by headache, dizziness, mental confusion, nausea, vomiting, and crampy abdominal pain, followed in a period of 24 hours to a week or two by evidences of serious damage to the kidneys and of lesser damage to the liver and other organs. Both the immediate and delayed effects may be observed, or either may occur without the other. It is generally believed that carbon tetrachloride is in part excreted unchanged and in part broken down within the body to form hydrogen chloride ( $\text{HCl}$ ) and phosgene ( $\text{COCl}_2$ ), which exert a local toxic effect in the tissues. Carbon tetrachloride is similar in action to chloroform, but its narcotic action is less pronounced, whereas its delayed toxic effects are more severe.

The toxic effects of carbon tetrachloride appear to be more severe in individuals with pre-existing pulmonary, renal, or cardiovascular disease. Excessive exertion, eating a large meal, or exposure to heat will aggravate the poisoning. Alcohol has a particularly marked influence on carbon tetrachloride poisoning. Individuals who have been drinking recently are more susceptible to the direct toxic effects of carbon tetrachloride, and habitual drinkers are more apt to develop severe toxic reactions.

Carbon tetrachloride exerts a toxic effect on the kidneys and liver, producing edema and fatty degeneration of the renal tubular epithelium and fatty degeneration and necrosis of the liver parenchyma, with impairment of function of both organs.

The myocardium may also be damaged following exposure to carbon tetrachloride, and sudden death from ventricular fibrillation may occur. The lungs also are irritated by carbon tetrachloride fumes. This irritation is generally not serious per se, but may lead to secondary bronchitis or bronchopneumonia.

Chronic exposure of the skin to carbon tetrachloride may lead to the development of an extensive dermatitis of the dry, fissured type. Liver enlargement and jaundice may also occur. However, liver cell involvement in either acute or chronic carbon tetrachloride exposure is accompanied by regeneration of new liver cells which

are more resistant to the effects of carbon tetrachloride, so that repeated exposures tend to increase one's resistance to this agent. A possible exception to this rule may be present in instances where exposures are so frequent that there is insufficient time for regeneration of liver cells.

**Symptoms.** The symptoms of carbon tetrachloride poisoning depend in great measure on the route of entry of the substance. Ingestion of carbon tetrachloride generally results in the usually described picture of severe gastrointestinal disturbances followed by jaundice and other evidences of severe liver damage. Inhalation of carbon tetrachloride fumes, the more important and more common source of carbon tetrachloride poisoning, may produce immediate symptoms or may not cause any outward effects for 24 hours or longer. The immediate effects, if any, are headache, dizziness, nausea, abdominal pain, and occasionally diarrhea. These gradually subside, but nausea, anorexia, and headache may persist. Kidney damage is frequent following inhalation of carbon tetrachloride vapor, and is characterized by renal failure which may progress to uremia and death or which may be reversible. There may be no immediate effects, but a few days after exposure oliguria may occur, accompanied by the presence of casts, albumin, and red blood corpuscles in the urine. There is retention of nitrogenous wastes, and the blood pressure usually rises. Death from renal failure may ensue. Individuals who recover usually show a pronounced increase in urinary output about two weeks after exposure, accompanied by a gradual return of the blood urea nitrogen to normal and subsequently a fall in blood pressure to the levels noted prior to exposure. It requires six weeks to two months for complete reversal of the kidney damage. Liver damage with jaundice may also occur, but is not always encountered.

**Diagnosis.** The diagnosis of carbon tetrachloride poisoning is easy if a history of exposure is obtained. It may be quite difficult in patients who develop signs of kidney failure and/or liver damage several days after their exposure has been forgotten. It should be suspected in persons who develop otherwise inexplicable concomitant signs of renal failure and subclinical liver damage. Specific questioning as to possible exposure to carbon tetrachloride in any patient with unexplained kidney and/or liver damage will bring to light cases which otherwise would be missed.

Diagnostic importance has been attached to the presence of narrowing of the visual field, especially for color vision; this may be a valuable aid in establishing the diagnosis in doubtful cases.

**Treatment.** The treatment of acute carbon tetrachloride poisoning should be instituted at once. The individual should be removed from the contaminated atmosphere whether unconscious or not. Artificial respiration should be carried on if normal respiration ceases, and oxygen administered if needed. Epinephrine should *not* be given, as it may precipitate a fatal attack of ventricular fibrillation. Any clothing wet with carbon tetrachloride should be removed at once, as it can be a potent source of further exposure.

Once exposure has been eliminated and the immediate acute effects of the agent combated, further therapy should be aimed at maintaining adequate kidney and liver functions. This can best be accomplished by supplying an adequate fluid and dietary intake, but this may be difficult to achieve in the face of continuing loss of appetite and nausea. The victim should be kept at rest and watched closely for about two weeks. If the urine output is reduced or if jaundice develops, therapy should be aimed at maintaining a normal electrolyte balance and protecting the liver with a high carbohydrate and moderate protein intake. Added choline or methionine may be of value. Inasmuch as protein will protect the liver but will increase the retention of nitrogenous wastes, nice clinical judgment as to which is more important is required. In general, therapy should be directed primarily at the kidneys. During the period of impaired renal output care must be taken to keep fluid administration at a level which will provide for the metabolic needs of the patient without producing edema and further kidney damage. If anuria should persist more than two weeks, or if the patient's condition becomes grave, then the use of an "artificial kidney" should be considered. Cases must be individualized, and definite rules obviously cannot be established.

## CYANIDE INTOXICATION

Hydrocyanic acid gas and related compounds which break down in the body to release hydrogen cyanide are probably the most rapidly acting poisons encountered. The toxic effects of the cyanide ion are dependent on its extreme affinity for the iron-containing respiratory enzymes, which combine with cyanide and are therefore

unavailable for oxygen transport. Cyanide produces an asphyxial death despite full saturation of the blood by oxygen. The carotid body and respiratory center are especially sensitive to the cyanide ion.

**Etiology.** Cyanide poisoning is not frequent. It occurs most often as a result of accidental or deliberate ingestion of potassium cyanide. Occasional instances of accidental cyanide poisoning occur following the injudicious use of hydrogen cyanide as a fumigant, although this type of fumigation is safe and effective in skilled hands, and is commonly used in industry. Adequate gas masks are available, but toxic quantities of the gas may be absorbed directly through the skin if the concentration is high. Cyanides are seldom employed by criminals for poisoning because of their extremely rapid action. A few states use hydrogen cyanide to execute condemned prisoners, however, for this same reason.

**Toxicology.** Following inhalation or ingestion of cyanide, tissue respiration is blocked. The rate of progression of cyanide poisoning depends on the dose of cyanide encountered. Large doses may lead to almost immediate loss of consciousness, followed by convulsions and death within 2 to 10 minutes. Ordinarily, several minutes elapse after the poison is taken before any effect is noted; then vertigo, mental confusion, headache, and palpitation are noted, followed by severe dyspnea, loss of consciousness, and convulsions. Death occurs in 15 minutes to one hour, as a result of respiratory arrest followed by cardiac arrest. The mortality rate following ingestion of cyanide is about 95 per cent, but recovery is likely unless death occurs in the first hour, as the cyanide ion is spontaneously and rapidly oxidized within the body to relatively harmless thiocyanates. Recovery is usually followed by persistent headache, tremor, and weakness. Irreversible cerebral damage may occur as a result of prolonged cerebral asphyxia.

The post-mortem findings in death due to cyanide poisoning are characteristic. A bitter almond odor is noted on opening the body. The blood remains fluid, and is generally bright red in color due to its high oxygen content. The presence of the cyanide ion may be demonstrated by chemical tests.

**Diagnosis.** A diagnosis of cyanide poisoning may be established clinically by the characteristic bitter almond odor and the extremely rapid

onset of symptoms. The diagnosis must be established almost immediately to be of any aid, as any therapy must be instituted almost at once if it is to be of benefit.

**Treatment.** As noted, treatment must be instituted rapidly to be of any benefit. The aims of therapy are threefold: to remove the already absorbed cyanide from the tissue respiratory enzymes by supplying methemoglobin; to remove or destroy by oxidation the cyanide in the gastrointestinal tract; and to provide general supportive measures. The tissue asphyxia may be relieved by the production of even slight degrees of methemoglobinemia, as methemoglobin firmly binds the cyanide ion to form the relatively stable cyanhemoglobin, thereby freeing the respiratory enzymes of the tissues. Methemoglobinemia may be induced by the intravenous injection of 1 per cent sodium nitrite or methylene blue, or by the inhalation of amyl nitrite. Five per cent sodium thiosulfate may also be injected intravenously, but is less effective. The removal or destruction of the cyanide remaining in the stomach can be accomplished by the oral administration of animal charcoal, 1:5 hydrogen peroxide, 1:1000 potassium permanganate, or 5 per cent sodium thiosulfate. General supportive measures such as maintenance of warmth and rest should be supplemented by administration of oxygen or, better, oxygen containing 5 to 7 per cent carbon dioxide. Artificial respiration may occasionally be of value. It is, of course, obvious that the individual (and the rescuer!) must be removed from the contaminated atmosphere if the poisoning is due to hydrocyanic acid gas.

## BARBITURATE INTOXICATION

The barbiturates are the most popular and widely used hypnotic and sedative drugs because of their efficiency, ready availability, ease of administration, and reasonable cost. They are still available by over-the-counter sale to laymen in many states, although the trend at present is toward state regulation restricting their distribution to prescription by physicians. They do not fall under the stringent control of the Harrison Narcotic Act. As a consequence, accidental and deliberate barbiturate intoxications are common, and the suicidal use of barbiturates is frequent. The clinically used barbiturates all produce central nervous system depression, the degree of depression varying with the dose administered from

mild sedation to deep coma. The only practical difference between the various enthusiastically advertised barbituric acid derivatives is their duration of action, which depends primarily on whether they are destroyed in the body (short-acting) or excreted in the urine (long-acting). All of the barbiturates occasionally produce irregular nervous system responses varying from excitement, hyperirritability, and convulsions to profound depression and coma after ordinary therapeutic doses; the aged being especially liable to such abnormal responses. Long-continued use of the barbiturates may lead to sensitization and the development of bizarre skin eruptions and/or fever.

**Toxicology.** The barbiturates are widely distributed throughout all tissues, but manifest their principal action on the brain. Excessive dosage leads to profound and prolonged coma and medullary depression characterized by fall in blood pressure, depression of heat regulation and consequent hypothermia, decrease in pulmonary ventilation, and finally respiratory paralysis. No organic brain changes can be demonstrated. Death usually occurs as a result of respiratory depression accompanied by bronchopneumonia.

**Acute Intoxication.** Acute barbiturate intoxication usually results from self-administration of excessive doses of the drug. The already stupefied, confused individual may take repeated doses at close intervals with no recollection of doing so. Excessive doses may be taken with deliberate suicidal intent, and in a few instances are given to others with homicidal intent. Therapeutic over-dosage also occurs, but is less common, as hypersusceptibility to the barbiturates is rare.

**SYMPTOMS.** The symptoms of acute barbiturate intoxication vary with the route of administration and the amount of the drug taken. Following oral or rectal administration, a dull sensation in the head and muscular incoordination are first noted. Impairment of smell and taste follow, with difficulty in swallowing. Nausea and vomiting may occur. The individual may or may not go through a state of excitement characterized by hallucinations and augmented motor activity prior to the onset of stupor. This is at first a fairly natural sleep from which the individual may be awakened, but progresses to deep coma from which the victim cannot be aroused. The pulse and blood pressure are well maintained unless the coma is deep and prolonged; then the respiration

becomes shallow and circulatory collapse may occur. The deep reflexes remain intact, but the superficial reflexes may be lost and the Babinski reflex positive. The presence of cyanosis, cold, clammy skin, and basal rales indicates a poor prognosis. Death may occur as a result of respiratory paralysis, but usually is due to circulatory collapse and atelectasis.

**DIAGNOSIS.** Barbiturate intoxication should be suspected in the presence of coma with normal temperature and quiet, regular breathing. A history of access to or use of barbiturates is helpful. The diagnosis can be proved with chemical tests, but these are tedious and require special techniques not generally available.

**TREATMENT.** Mild cases of barbiturate poisoning will respond to withdrawal of the drug and general supportive measures. More severe cases require active measures. The stomach should be lavaged, following which a saline cathartic should be left in the stomach. Emetics should be avoided. If the coma is deep, measures directed at improving pulmonary ventilation and oxygen exchange are of great value. Oxygen-carbon dioxide mixtures (95 per cent-5 per cent) should be administered, an adequate airway maintained, and the position of the patient changed frequently. Penicillin should be administered in adequate dosage to ward off secondary bronchopneumonia. Cerebral stimulants such as amphetamine, nikethamide ("Coramine"), caffeine, or ephedrine given every one to four hours may be of value. Amphetamine should be given intravenously if severe depression is present. It is about as effective as picrotoxin, and safer. Picrotoxin is a potent stimulant, but is not without danger. Only enough to improve the quality of the breathing and increase muscle tonus and reflex activity should be given. The exact dose cannot be stated; it should be given slowly or in divided doses until the desired effect is achieved. Attempts to return the patient to consciousness with picrotoxin will lead to convulsions. The use of intravenous sodium succinate solution has been reported to be effective in combating barbiturate intoxication. While its use is rational from a biochemical standpoint, it has been generally disappointing clinically.

**Chronic Intoxication.** Chronic barbiturate intoxication (barbiturism) is encountered in emotionally unstable or neurotic individuals. The use of the drug usually starts with chronic insomnia, and is continued in an effort to produce peace of

mind or euphoria. Occasional individuals indulge in barbiturate "sprees." Tolerance does not develop, and there are no organic withdrawal symptoms.

**SYMPOTMS.** Chronic barbiturate poisoning is characterized by vertigo, ataxia, nystagmus, mild dementia, visual hallucinations, muscular tremors, poor memory, slowness of thought, and thickness of speech. Variable reflex changes may occur, and mental aberrations simulating acute psychoses or delirium tremens are occasionally encountered. Anemia and porphyrinuria have been reported.

**DIAGNOSIS.** There is no characteristic clinical picture, and the diagnosis generally is established by a history of the use of the drug.

**TREATMENT.** Recovery follows withdrawal of the drug, but may take as long as 10 weeks to be complete. Relapses are frequent unless the underlying emotional instability is treated with adequate psychotherapy.

#### CARBON MONOXIDE INTOXICATION

Carbon monoxide is a colorless, practically odorless gas produced by the imperfect combustion of carboniferous materials. It is not ordinarily present in nature, but is probably the most important and widely encountered toxic agent except alcohol which has been deliberately ingested. Carbon monoxide is present in high concentration in wood smoke, in gasoline engine exhaust, and, to a lesser extent, in Diesel engine exhaust. It is produced in many industrial processes. One extremely important source of carbon monoxide which is responsible for many deaths is artificial gas, which contains a considerable concentration of carbon monoxide. Natural gas does not contain carbon monoxide, but carbon monoxide poisoning may occur in homes which are supplied with natural gas, as carbon monoxide is produced by its incomplete combustion.

**Etiology.** Carbon monoxide is an asphyxiant poison; it acts by virtue of its ability to exclude oxygen from the tissues. Carbon monoxide has an affinity for hemoglobin about 200 to 250 times that of oxygen, so it excludes oxygen from the blood by the formation of carboxyhemoglobin. Carbon monoxide also causes a marked shift to the left of the dissociation curve of the remaining oxyhemoglobin, so that the oxygen still present in the blood is not available to the tissues (see Chapter 12).

The relative amounts of carboxyhemoglobin and oxygenated or reduced hemoglobin present in the blood stream are governed by the concentrations of carbon monoxide and oxygen in the atmosphere to which the blood is exposed and the relative affinity of hemoglobin for the two gases. It is also influenced, however, by the duration of exposure to the gases, as considerable time is required for the blood to reach maximum saturation with CO. The time required for the blood to become maximally saturated when a given concentration of carbon monoxide is inhaled is indeterminate, as full saturation is approached only gradually, the rate decreasing as the saturation increases. The time required to reach half the maximum possible saturation for a given degree of exposure is fairly definite, however; it is approximately one hour for an average-sized man at rest. Individuals who are actively exercising reach half saturation more rapidly, as do children or small animals. In fact, the rapid carbon monoxide uptake of mice or canary birds is used as a crude warning system to indicate the presence of dangerous conditions before men have had time to reach a dangerous level of carboxyhemoglobin in the blood.

Following withdrawal from exposure, carbon monoxide gradually is eliminated from the blood. Practically all of the carbon monoxide absorbed by the body is eliminated via the lungs. This takes place fairly rapidly at first, and then at a gradually diminishing rate as the blood level falls. Carbon monoxide elimination depends on its being displaced from hemoglobin by oxygen, and proceeds slowly. It can be greatly accelerated by the inhalation of high concentrations of oxygen, however, because of the increased mass action of the higher concentration; and also by the inhalation of 5 to 10 per cent carbon dioxide, because of the increased ventilation and consequent reduction in partial pressure of carbon monoxide in the lungs and the additional increased dissociation of carboxyhemoglobin produced by carbon dioxide.

The American Standards Association and various states have recognized 100 parts per million parts of air as the maximum concentration of carbon monoxide to which workers should be exposed for an eight-hour working day. The absence of any injury to health in Holland Tunnel traffic officers exposed over a 13-year period to an average of 70 parts per million is particularly striking evidence in support of this limit.

**Toxicology : ACUTE EFFECTS.** The acute effects of breathing carbon monoxide depend on the per cent saturation of hemoglobin with carbon monoxide and the degree of activity of the individual, and will therefore be influenced by the concentration of carbon monoxide inhaled and the duration of the exposure.

The inhalation of relatively high concentrations of carbon monoxide (above 0.5 per cent) results in rapid collapse, loss of consciousness, and death within a few minutes unless exposure is interrupted. In the event of survival there may be nausea, dizziness, headache, and even convulsions persisting for several days or more.

Exposure to lesser concentrations (0.05 to 0.1 per cent) results in a gradually increasing series of symptoms occurring as a result of the progressive asphyxia which develops. At first, respiration is increased, although this is generally not recognized by the victim or by others. Later, the individual becomes aware of a severe frontal headache, a feeling of constriction about the temples, nausea, mental confusion and, in some instances, hallucinations. Retrosternal and precordial pain may be present. If exposure is severe or long continued, the individual may progress to a state of muscular weakness and incoordination, particularly of the legs, and the respirations become irregular and shallow. Loss of consciousness may occur, followed by cessation of respiration and death. The individual at first appears pale, but as the condition progresses the skin and mucous membranes may appear cherry red, even when respiration has ceased. There is a marked variation in the clinical symptoms of individual cases.

Recovery in nonfatal cases occurs with gradual retrogression of the symptoms which occurred as the case developed, as the carboxyhemoglobin in the blood gives up its carbon monoxide and becomes available for oxygen transport. Elimination of carbon monoxide proceeds rapidly while the blood concentration is relatively high, and continues at a decreasing rate as the concentration in the blood approaches zero.

Acute carbon monoxide poisoning may occasionally be followed by serious sequelae, although recovery is complete in most instances. Sequelae developing after carbon monoxide poisoning generally appear after a clear interval of one to three weeks. They are the result of irreversible tissue damage, usually in the central nervous system,

and are characterized by neuropathies and motor or mental changes occurring as a result of brain damage. Occasionally, Parkinson's syndrome or a series of symptoms similar to multiple sclerosis may be encountered. Cases with definite sequelae are rare, however, as the margin between instances with no permanent tissue damage and instances with damage which is necessarily fatal apparently is extraordinarily small. Such aftereffects never appear unless the poisoning has been extremely severe.

Individuals dying of acute carbon monoxide poisoning exhibit fairly characteristic findings, consisting of intense congestion of the brain and meninges which involves both arteries and veins. The cut surface of the brain appears as though stained with eosin because of the intense congestion and the color imparted by the carboxyhemoglobin. The lungs, spleen, and heart muscle are also intensely congested. In addition, there is marked edema, particularly throughout the brain, where it is perineuronal and perivascular in distribution. There is also widespread nerve cell damage of variable degree, most severe in the cortex, corpus striatum, dorsal vagal nuclei, and dorsal areas of the medulla.

**CHRONIC EFFECTS.** Carbon monoxide is not a cumulative poison, and all inhaled carbon monoxide can be ventilated out of the blood. The gas, *per se*, does not damage tissues, blood cells, or the hemoglobin with which it combines in the body. Therefore, no such condition as chronic carbon monoxide poisoning can exist. Numerous reports of chronic carbon monoxide poisoning are encountered, however, for various reasons. Most of these represent sequelae from severe acute cases. A few, such as the anemias occasionally reported after exposure to carbon monoxide, may be due to other toxic agents inhaled along with carbon monoxide. As a matter of fact, repeated exposure to low concentrations of carbon monoxide may produce a compensatory increase in red blood count similar to that noted in individuals exposed to reduced oxygen pressures while living at high altitudes.

There is no doubt that repeated exposure to low concentrations of carbon monoxide can result in lassitude, headache, and digestive disturbances, but these are the result of repeated bouts of oxygen deprivation and represent the effect of repeated mild acute poisonings rather than a true chronic effect of carbon monoxide. Central nerv-

ous system damage following repeated bouts of anoxia due to repeated carbon monoxide exposure may occur, and may be considered a form of chronic carbon monoxide poisoning.

**Diagnosis.** Carbon monoxide poisoning can generally be recognized by the circumstances surrounding the case. The presence of a cherry red color in the skin and blood are characteristic. Chemical tests which are fairly simple to perform when the appropriate apparatus is available can be made on the blood or expired air of suspected victims. Such tests should be carried out promptly, however, as carbon monoxide is eliminated from the blood fairly rapidly. Such evidence should be obtained whenever possible, as it may be of medicolegal significance.

**Treatment.** All therapy of carbon monoxide poisoning should be directed at elimination of the gas from the blood stream. The victim should be removed from the contaminated atmosphere and kept warm and at rest. If there is loss of consciousness and depression, or interruption of breathing, then artificial respiration should be administered. In any case, the victim should be given oxygen containing 5 to 7 per cent carbon dioxide by mask. The oxygen will increase the rate of elimination of carbon monoxide by mass action, and the carbon dioxide will be of additional value because it will stimulate the respiratory center and increase pulmonary ventilation, thereby promoting the elimination of carbon monoxide from the air in the lungs, and will also increase the dissociation of carboxyhemoglobin.

Individuals with milder degrees of carbon monoxide poisoning who have not lost consciousness should be kept at rest. The administration of oxygen and carbon dioxide to these individuals will greatly accelerate their elimination of carbon monoxide and will aid in reducing or eliminating the unpleasant headache and digestive symptoms accompanying the moderate anoxia present during the gradual elimination of carbon monoxide from the body.

#### INTOXICATION BY MORPHINE AND RELATED ALKALOIDS

Opium and its derivatives are the most important alkaloids, from both the therapeutic and the toxicologic standpoint. Opium and its principal derivatives, morphine, codeine, dihydromorphinone hydrochloride, and heroin all act more or less similarly; their primary action is depression

of the awareness of discomfort and pain. Large doses produce an irregularly descending depression of the brain and medulla, and a concomitant stimulation of the spinal cord. Unfortunately, opium and its derivatives frequently produce both acute and chronic intoxication. The opium problem is immensely aggravated by the tendency of these drugs to produce addiction.

**Acute Opium Intoxication.** Acute intoxication by opium or one of its derivatives presents a similar picture in both the nonaddict and the addict. Acute intoxication is generally not encountered in the addict who is tolerant to the drug, but is fairly frequent among addicts who have abstained for a few weeks, lost their tolerance, and then taken the same dose which previously produced euphoria, but which now results in serious poisoning.

**SYMPTOMS.** The symptoms of acute intoxication range from giddiness, euphoria, flushing, pleasant bodily sensations, lassitude, and incoordination to coma with slowing of the pulse and respiration. Nausea and vomiting are frequent, and itching of the skin and nose commonly occur. If the administered dose is especially large, the earlier symptoms may be minimal, the individual rapidly progressing to coma with markedly slowed and shallow respirations. The pupils are pin-point. Cyanosis, asphyxial convulsions, and dilatation of the pupils may occur in the late stages, and are grave prognostic signs. Pulmonary edema is occasionally encountered and is frequently a terminal event.

There is a considerable individual variation in response to a given dose of any opium derivative. Some individuals may develop intractable nausea and vomiting, while others may become agitated or even maniacal when given ordinary therapeutic doses of the drugs. Persons with severe anemia, hypothyroidism, or adrenal insufficiency are extremely sensitive to morphine and other opium derivatives, and may develop coma after ordinary doses. Persons with severe liver damage tolerate morphine poorly, as the liver is the chief organ of detoxification.

Recovery from acute opium intoxication, either spontaneously or as a result of treatment, occurs in the course of a day or two. The respiration and pulse gradually improve, and consciousness returns. Mental depression, confusion, headache, itching of the skin, and constipation may persist for several days.

**DIAGNOSIS.** The diagnosis usually is fairly simple if a history of the use of opiates is obtainable. The clinical picture in slowly developing cases is fairly clear, but in individuals receiving massive doses it may progress so rapidly as to be puzzling. The pin-point pupils are highly characteristic and, although not pathognomonic, are of distinct aid, especially in the presence of respiratory depression and slight or moderate cyanosis. Some addicts may also use atropine to obscure the pin-point pupils, however, so dilated pupils cannot be depended on to rule out opiate intoxication. The diagnosis may be established by the recovery of the offending drug in the urine, but this is time-consuming and requires special technics not generally available.

**TREATMENT.** The treatment of acute opium intoxication should be directed into three channels: removal or neutralization of the drug remaining in the gastrointestinal tract, prevention of respiratory failure, and avoidance of circulatory collapse. The stomach should be thoroughly lavaged with several quarts of a 1:5000 potassium permanganate solution, following which a suspension of charcoal (50 ml. of 20 per cent suspension) and/or a saline cathartic (50 ml. of 50 per cent Epsom salts) should be introduced through the stomach tube and left in the gastrointestinal tract. Respiratory failure can best be combated by the administration of 90 per cent oxygen and 10 per cent carbon dioxide, by the use of repeated intramuscular injections of caffeine and sodium benzoate (0.5 to 1 Gm.) or intravenous nikethamide (5 ml. of 25 per cent solution). The use of a Drinker respirator may be lifesaving in occasional severe cases. Circulatory collapse can best be prevented by maintaining adequate oxygen exchange by the methods outlined above. The use of amphetamine sulfate may also be of benefit. Atelectasis and secondary bronchopneumonia are not infrequent as a result of the reduced respiratory exchange. It is therefore desirable to administer penicillin to all cases with coma of more than a few hours' duration.

**Opiate Addiction (Chronic Opiate Intoxication).** The opiates, especially morphine, heroin, dihydromorphinone hydrochloride, and also the synthetic drugs isonipecaine ("Demerol Hydrochloride"), methadon hydrochloride, and metopon hydrochloride may all produce serious addiction. Practically all, if not all, drugs which are capable of alleviating visceral pain also are capa-

ble of causing addiction, although primary addiction to codeine is doubtful and secondary addiction is rare. The addiction produced by the opiates apparently is a result of the euphoria, contentment, and escape from reality which they induce. The problem of addiction is immensely complicated by the development of tolerance, with its need for a large dose to produce the same effect, and of dependence, with the occurrence of withdrawal symptoms. The morphine addict may tolerate as much as 4 Gm. of the drug each day, enough to kill 15 nonaddicted adults; the addict may appear quite normal as long as he receives his daily dose of the drug, but will undergo intense suffering and may die if the drug is withheld. Because of the difficulty of obtaining the drug the addict may switch from one opiate to another. Marked cross tolerance exists, and the craving can be satisfied to some extent by any member of the series. The more potent drugs are, however, more satisfying to the addict.

The greatest tragedy of opiate addiction is the moral disintegration brought about by the habit. All normal drives and instincts are subordinated to the necessity of obtaining the drug. The addict with ready access to opiates may lead a fairly normal social existence, but he will pursue a completely ruthless course in his quest for the drug, regardless of consequences; the moral fiber is sapped, and lying, cheating, and stealing are to him justifiable means to the end of obtaining more drug. On the other hand, it must be emphasized that the mental faculties and personality of the addict are unchanged if he does obtain the drug.

**ETIOLOGY.** The factors responsible for the development of addiction are not entirely clear. Certain facts, however, are evident. Addiction is more commonly induced by the more potent opiates—morphine and, especially, heroin. Addiction is far more likely in the emotionally unstable, the neurotic, and the adolescent. Psychopaths are especially apt to become and remain addicted. Addiction is more likely among individuals with ready access to the drugs (physicians, nurses, etc.).

An appreciable percentage of addicts develop their habit as a result of having received the drugs on the prescription of a physician for the relief of pain. Many addicts, however, have begun the habit as a result of a desire for euphoria, or out of sheer curiosity. Contrary to popular belief, many

addicts are highly intelligent individuals. Such persons may successfully conceal their habit for years if they can obtain sufficient amounts of the drug. Also, the addict with a fairly normal personality will stabilize on a fairly reasonable daily dose (15 to 60 mg. several times a day), whereas the psychopath will continue to increase his dose and therefore become unable to obtain sufficient amounts of the drug to satisfy his craving.

**SYMPTOMS.** The symptoms of morphine addiction per se, except for the withdrawal symptoms attendant on failure to obtain the drug, are not marked. The addict who can obtain an adequate supply of the drug may appear entirely normal. In time, however, ambition and efficiency are lost, and wide swings in mood ranging from euphoria to extreme depression may be encountered. Many addicts must concentrate all their efforts on obtaining the drug, with consequent evident moral and economic deterioration. They become careless and sloppy in appearance, and resent the attitude of society toward their problem.

The addict frequently exhibits pin-point pupils, although some avoid this by the use of atropine. Digestive disturbances, especially severe constipation with fleeting episodes of diarrhea, are common. Nutritional disturbances and vitamin deficiencies may develop as a result of the inability or unwillingness of the addict to spend money for adequate food. There is no pathognomonic pattern, however, which brands the addict. He appears most abnormal when his supply of the drug is cut off, and may seem entirely normal when it can be obtained.

Many addicts exhibit multiple abscess scars as well as induration and pigmentation of the skin as a result of failure to use adequate asepsis when administering the drug.

**WITHDRAWAL SYMPTOMS (DEPRIVATION SYNDROME).** The withholding of opiates from the addict results in the development of a definite train of symptoms which vary in intensity with the degree and duration of the addiction. Early addicts develop yawning, restlessness, sweating, lacrimation, and rhinorrhea. These are unpleasant but endurable, and disappear in a few days if the drug is completely withheld. More confirmed addicts become uneasy and irritable, yawn and sneeze spasmodically, lose their appetite, and develop vomiting and diarrhea. The voice becomes hoarse, and the eyes and nose run profusely. The

more severe addict may, in addition to these symptoms, develop extreme weakness, muscular tremors, marked insomnia, and severe dehydration. He appears gaunt and drawn. Acute mania may occur. Finally circulatory collapse may occur, with severe sweating, a weak, irregular pulse, and prostration. Death may ensue unless 10 mg. of morphine is administered at this time.

Complete withdrawal results in an increase in the severity of the symptoms for about three days, and then in a gradual decline in their severity for a week or 10 days.

**TREATMENT.** The treatment of choice for chronic opiate intoxication is complete, sudden withdrawal of the drug, or at least rapid reduction in dose levels. In a few instances it may be desirable to substitute isonipecaine for a short period, in order to reduce the intensity of the final break with the drug. Withdrawal must be carried out under strict surveillance, in a hospital or other institution, as the addict cannot resist his craving.

Gradual withdrawal is generally less effective than the abrupt or rapid deprivation of the drug, and the total suffering of the individual is about the same. Marked restlessness may be combated by sedative baths or by the use of barbiturates, chloral, or paraldehyde. Fluid balance should be maintained by the use of intravenous fluids.

After a few days, or at least one or two weeks, the craving is lost, and the addict is temporarily cured. Unfortunately, the cure is seldom permanent; only 2 to 5 per cent remain cured for five years, the average duration of cure being only two years. Once a temporary cure has been established, thorough psychiatric care and guidance are essential. Even these are ineffective for the psychopath. The ex-addict clearly remembers the euphoria which morphine produced, and any pain or unpleasant situation awakens the dormant desire. It is especially important that the medicinal use of opiates be curbed in the ex-addict, as many succumb again via this route through the carelessness or unawareness of physicians.

## METAL POISONING

Serious poisoning may follow the ingestion or inhalation of a variety of metals or metallic compounds. Recent studies suggest that the toxic action of most metals results from the formation of organometallic complexes involving adjacent sulfhydryl groups of protein molecules, with subse-

quent interference with normal cellular metabolism and injury or death of the involved cells. The nature and severity of the poisoning depend on a variety of factors, the most important of which are the metal involved, the form in which it is encountered, and the duration and degree of exposure. Most metallic poisons are capable of producing both acute and chronic poisoning, but chronic metal poisoning is by far the most important.

The signs and symptoms of metal poisoning vary greatly, depending on the particular substance involved, and must be considered individually. The treatment of poisoning by various metals also must be individualized according to the metal involved and the nature and severity of the poisoning. There is available, however, a reasonably specific antidote for certain types of metal poisoning which deserves special emphasis. This substance is BAL (for "British anti-lewisite"), which was discovered by the British during World War II in the course of an intensive search for an effective antidote for burns produced by arsenic-containing war gases such as lewisite. Chemically, BAL is 2,3-dimercaptopropanol (dimercaprol). The presence of two sulfhydryl groups in the molecule results in its being a highly reactive substance which will combine with a number of metals both in vitro and in vivo to form reasonably stable BAL-metal complexes. The effectiveness of BAL as an antidote for various types of metal poisoning is dependent on the greater affinity of the metal for BAL than for the tissues being poisoned. At least many of the effects of metals on the body are the result of their combination with thiol groups on protein molecules, resulting in an alteration of the metabolic activity and viability of the tissue. BAL is capable of forming reasonably stable, soluble complexes with a variety of metals, and thereby stripping the metal from the poisoned tissue.

BAL is most effective in poisoning due to arsenic, mercury, and gold. It is of some benefit in experimental poisoning due to cadmium, antimony, and zinc. BAL therapy appears to be ineffective in lead poisoning, argyria, and poisoning due to thallium, selenium, and tellurium.

BAL is available in solution in combination with peanut oil and benzyl benzoate. It is administered intramuscularly at intervals ranging from every two hours to once daily in doses of 2.5 to 5 mg. per kg. of body weight, depending on

the severity of the poisoning and the metal involved. BAL itself is an unpleasant-smelling, irritating substance which can produce definite toxic effects when given in the higher dosages.

The more important metallic poisons will be considered individually because of the wide variation in clinical picture, severity, and importance.

**Arsenic Poisoning.** Arsenic poisoning usually results from exposure to one of the more soluble oxides or salts of arsenic. Arsenic poisoning may occur in industry, especially the copper-refining and chemical industries; in agriculture, following the use of arsenical sprays or dusts; and in the home, from the ingestion of rat or fly poisons, from cosmetics, or from plant sprays, all of which may contain arsenic. Arsenic poisoning may also follow the use of organic arsenical drugs in the treatment of syphilis or other protozoan infestations.

The inhalation of arsine gas (arseniuretted hydrogen,  $\text{AsH}_3$ ) results in serious poisoning which differs in all respects from other types of arsenic poisoning, and will be discussed separately (see p. 750).

Arsenic compounds exert their most serious effects following absorption via the gastrointestinal tract or lungs. The more soluble arsenic compounds are more toxic, as they are more readily absorbed. As little as 65 mg. of  $\text{As}_2\text{O}_3$  may be fatal. Arsenic compounds produce severe dermatitis and even ulceration of the skin following prolonged or repeated contact. Mucous membrane irritation also occurs, and perforation of the nasal septum is common among workers exposed to arsenic oxide dusts. Arsenic is slowly excreted from the body, in large part via the skin and its appendages, so repeated small doses may exert a cumulative effect.

**CLINICAL COURSE.** The clinical course of arsenic poisoning will depend on the type of arsenic compound encountered and the degree of exposure, and is quite variable. Acute arsenic poisoning usually follows the ingestion of an inorganic arsenic compound, and is characterized by profuse, persistent vomiting and diarrhea. Dizziness, headache, and painful sensations in the extremities also may occur. Death occurs in a considerable number of cases as a result of exhaustion due to the prolonged gastroenteritis. Subacute poisoning is characterized by gastroenteritis of lesser degree, accompanied by inflammation of mucous membrane surfaces, resulting in conjunctivitis,

stomatitis, and pharyngitis. Skin eruptions also develop in time. Polyneuritis may occur, but the neurologic findings are not specific. Chronic arsenic poisoning may be most puzzling, resulting in skin rashes, hyperkeratoses, and melanosis of the skin; and also in polyneuritis with muscle atrophy and sensory disturbances. Bone marrow damage, characterized by anemia or leukopenia, may also occur. Inorganic arsenic compounds are more likely to cause skin changes, polyneuritis, and leukopenia; whereas organic arsenicals are prone to produce severe fatty degeneration of the liver and even acute, fatal hepatitis, as well as depression of all bone marrow elements, resulting in leukopenia, thrombocytopenia, and erythrocytopenia.

**DIAGNOSIS.** The diagnosis of arsenic poisoning can be made more readily if the working conditions and possible chemical exposures of the patient are studied. Once suspected, the diagnosis can be confirmed by the finding of abnormally high levels of arsenic in the urine, hair, or nails. The arsenic content of the hair and nails reflects the patient's exposure to arsenic at the time the deposits were formed, however, and so will be of little or no value in acute or recent cases.

**TREATMENT.** The treatment of arsenic poisoning consists of withdrawal from exposure and, in acute or severe cases, the prompt and continued administration of BAL (3 mg. per kg. of body weight, every four to six hours for two to three days, then twice daily for 10 days or until recovery).

**ARSINE POISONING.** Poisoning by arsine ( $\text{AsH}_3$ ) differs from other types of arsenic poisoning. Arsine is a highly toxic gas which produces an intense hemolysis of red blood corpuscles, and may also inhibit tissue respiration. Clinical arsine poisoning is characterized by malaise, vertigo, weakness, headache, and nausea three to six hours after the gas is inhaled. This is followed in a few hours by hemoglobinemia, hemoglobinuria, and proteinuria. Collapse and early death may occur, or the patient may develop the clinical picture of a lower nephron nephrosis as a result of the precipitation of hemoglobin in the renal tubules. The mortality rate of arsine poisoning is high (about 30 per cent), and recovery is slow. BAL is ineffective in the treatment of arsine poisoning.

**Beryllium Poisoning.** Serious poisoning by beryllium has become increasingly important in recent years as a result of the increasing use of

this substance in atomic energy development and as a constituent of the powders used in fluorescent lamps. The varieties of poisoning produced by beryllium depend primarily on the type of exposure. Workers exposed to moderately high concentrations of beryllium dust in the processing and refining of this metal, or in its use in atomic research, may develop an acute infiltrative pneumonitis lasting several weeks, which may terminate fatally or progress to complete recovery. Workers exposed to fluorescent lamp powders containing beryllium have developed a granulomatous pulmonary reaction characterized by extreme dyspnea and weakness which clinically and radiologically resembles Boeck's sarcoid. This disease may not become manifest until many months after exposure to beryllium dust has terminated, and may persist for months or years, ending in recovery or death from intercurrent respiratory infection. Finally, chronic granulomatous lesions have been reported at or near the site of wounds contaminated by beryllium-containing dusts. The risks involved in the disposition of old fluorescent light tubes is apparent. Cuts contaminated by the fluorescent powders should be carefully and thoroughly cleansed and debrided.

The mechanism of the granulomatous tissue reactions produced by beryllium are not clearly understood, but they appear to be a gradual cellular reaction to the presence of beryllium somewhat analogous to the type of tissue reaction produced in the presence of silica.

**Cadmium Poisoning.** Cadmium poisoning is infrequently encountered, but may be extremely severe. The ingestion of food or liquid contaminated by cadmium (which may occur when acid foods are prepared in cadmium-lined containers) results in a severe gastroenteritis characterized by sudden onset of nausea, vomiting, severe crampy abdominal pain, and diarrhea. Serious poisoning by cadmium may also follow the breathing of freshly formed cadmium oxide fumes. This may happen when cadmium-plated steel is heated or welded in the absence of adequate ventilation. Cadmium oxide fumes are only slightly irritating when first inhaled, although slight eye irritation, dryness of the throat, and tightness in the chest may be noted. Four to eight hours after exposure, the victim develops increasing cough and chest pain, which progress to severe pulmonary edema with consequent frothy pink sputum and cyano-

sis. Abdominal pain, nausea, and vomiting may also be present. A considerable proportion of the reported cases have terminated fatally.

**TREATMENT.** The treatment of acute cadmium poisoning should consist of complete rest, oxygen, and other supportive measures. The status of BAL in acute cadmium poisoning is not clear. In experimental animals it may result in the amelioration of the pulmonary symptoms, but may be followed by renal failure due to precipitation of a relatively insoluble BAL-cadmium complex in the kidneys. On the basis of available reports it would appear that use of BAL would be justified in extremely serious cases of cadmium poisoning, but that the administration of BAL to such a patient, once started, should be continued at a high dosage level for several days in order to prevent or minimize the accumulation of cadmium in the kidneys. BAL and cadmium may combine in vivo to form a relatively insoluble equimolecular complex, or a more soluble complex made up of two molecules of BAL for each of cadmium. The latter is presumed to be formed when the dosage level of BAL is maintained at a high level.

**Gold Poisoning.** Poisoning by gold occurs only after its parenteral administration, usually as a soluble salt. The clinical manifestations of gold intoxication generally occur during the course of gold salt therapy, and should be carefully watched for in patients receiving gold parenterally. The most common and serious reactions involve the bone marrow, resulting in thrombopenia with bleeding phenomena or in leukopenia. Skin rashes are fairly frequent, and acute, severe, exfoliative dermatitis may develop. Evidences of kidney damage or gastroenteritis are occasionally encountered. Acute hepatitis may occur. BAL has been shown to be an effective antidote for acute gold poisoning occurring during the course of gold salt therapy.

**Lead Poisoning.** Lead is one of the most dangerous and insidious metallic poisons known to man. All forms of lead are potentially toxic, but lead poisoning most commonly occurs after the inhalation of lead fumes or finely divided lead dusts. Lead poisoning also follows the ingestion of food or drink contaminated with lead. The risk of poisoning increases with decrease in particle size or increase in the rate of solution of the lead compound encountered. Lead is a cumulative poison in every sense. Lead salts are stored in the body following absorption, and are excreted

slowly via the feces and urine. A single dose of a lead salt may cause no harm, whereas the same amount divided into twenty portions and taken on each of twenty consecutive days may produce serious poisoning.

Lead entering the body following ingestion is absorbed into the portal circulation, and some of the lead is taken up by the liver and excreted with the bile, whereas inhaled lead is absorbed directly into the general circulation; therefore the latter route of entry is more serious. Lead is distributed fairly evenly throughout all body tissues after absorption, but exerts its toxic effects on the blood, muscles, kidneys, and nervous system, while it has little if any effect on the bones, liver, and intestinal tract. An exception to this statement occurs in children, where epiphyseal growth may be seriously impaired as a result of lead poisoning.

The amount of lead present in the circulation is generally considered to determine whether lead poisoning will occur. Ordinarily, this is governed by the rate and duration of lead absorption. Interruption of this absorption usually results in a gradual drop in the amount of circulating lead and an amelioration of the symptoms of lead poisoning. The return of stored lead from the bones to the circulation, usually as a result of a temporary acidosis, may result in an increase in the circulating lead and an exacerbation of the poisoning. This is most often encountered during periods of intercurrent illness, such as pneumonia, and may seriously impede recovery.

The presence of increased lead absorption and excretion does not necessarily mean that lead poisoning is present. Many individuals with an abnormal intake and excretion of lead will continue to feel well and continue their usual activities. These persons should not be considered to have been poisoned; they can only be considered to have increased lead absorption. A diagnosis of lead poisoning should be made only in individuals who lose their sense of well-being and are ill as a result of their lead absorption.

**SYMPTOMS.** The symptoms of advanced lead poisoning are fairly typical, but early or mild lead poisoning may be extremely protean in its manifestations and easily missed. The classic symptoms and signs of lead poisoning involve the gastrointestinal tract, the nervous system, and the blood.

The gastrointestinal symptoms and signs in-

clude the so-called "lead line," actually a series of bluish dots occurring uniformly along the gingival margins, caused by the deposition of insoluble lead sulfide in capillary loops as a result of bacterial action, resulting in the characteristic dots. The presence or absence of a lead line depends as much on the oral hygiene of the individual as on the level of circulating lead; it may be present in persons with increased lead absorption but no evidence of lead poisoning, or may be absent in cases of severe lead poisoning. A similar line may occur in poisoning by other metals, notably bismuth. Other effects of lead on the gastrointestinal tract range from anorexia and vague discomfort to severe colicky pain and constipation. The colic of advanced lead poisoning is due to segmental spasm of the musculature of the large bowel.

The nervous system manifestations of lead poisoning range from mental depression to severe mania, the latter being infrequent. Children are especially prone to nervous system involvement, and may have epileptiform convulsions. Lead poisoning in children frequently leads to mental retardation and brain atrophy. Lead also affects the peripheral nerves, producing a painless and rapidly progressive paralysis of the involved muscles. Characteristically, the palsy of lead poisoning involves the muscles which are most used and most fatigued in the individual; hence the wrist drop of the painter, the scapulohumeral weakness of the laborer with a shovel, and the sartorius paralysis of the tailor. Remission of the weakness occurring as a result of lead poisoning is fairly rapid on withdrawal from exposure, but true paralysis may require weeks to months for complete recovery. Long-continued poisoning may result in permanent changes.

The blood usually shows characteristic changes in the presence of lead poisoning. There is usually moderate anemia, of 3,500,000 to 4,000,000 red corpuscles, which may be due primarily to increased brittleness of the cells and increased destruction in the circulation, although some authorities believe it to be a result of impaired formation of the iron-porphyrin complex or the production of protoporphyrin. It is accompanied by increased red corpuscle production, evidenced by small or moderate reticulocytosis and the presence of "stippling," a punctate basophilic granulation of the red corpuscles demonstrated by most of the commonly used differential blood stains.

The stippling is generally thought to represent degeneration of reticulated cells. The presence of stippling is not pathognomonic of lead poisoning, as it may occur in the presence of severe infections, leukemia, pernicious anemia, or Mediterranean anemia, or occasionally in normal individuals; but the presence of a high stipple cell count is strong evidence of active lead poisoning.

**DIAGNOSIS.** The diagnosis of lead poisoning should be established early, in order to permit withdrawal from exposure before any irreversible changes have occurred. This is not easy. Many other conditions may be confused with lead poisoning. It should be emphasized that the presence of illness in a worker who has some exposure to lead does not indicate that he is suffering from lead poisoning. Unfortunately, it is not uncommon to find many other conditions erroneously diagnosed as lead poisoning and improperly managed merely because a history of possible lead exposure was obtained. The following investigations should be undertaken to substantiate a diagnosis of lead poisoning:

1. Inquiry into time and place of exposure, with substantiation of conditions.
2. Examination for any of the characteristic symptoms or signs of lead poisoning.
3. Examination of the blood, with particular attention to the red corpuscle count and the presence of basophilic stippling.
4. Analysis for lead of a 24-hour sample of urine or of a blood sample. The urine must be collected in a chemically clean container. Spot urine samples may be used, provided appropriate volume corrections are made, but are less accurate. The finding of more than 0.10 mg. of lead per liter of urine in a 24-hour specimen, or of more than 0.05 mg. of lead per 100 ml. of whole blood in an individual with symptoms of lead poisoning clinches the diagnosis.

**TREATMENT.** The treatment of lead poisoning consists of withdrawal from all exposure to lead, symptomatic supportive measures, and promotion of lead elimination from the blood stream. Most patients with lead poisoning will recover spontaneously if exposure is interrupted. Lead colic may be of sufficient severity to require active treatment. Intravenous calcium gluconate usually results in the relief of the colic for several hours. It should be followed by the administration of a saline cathartic. Atropine or nitroglycerin may also provide relief of lead colic. Mor-

phine is seldom needed, and is less effective than would be expected. During the acute phase of lead poisoning the calcium intake should be maintained at a high level in order to drive the lead out of the blood stream into the bones. Once the acute symptoms have subsided, it may be desirable to promote lead excretion (deleading) by the administration of a low-calcium diet and acid-producing salts, such as ammonium chloride (6 to 8 Gm. daily) in order to promote a negative calcium balance and rapid release of stored lead from the bones. Aub recommends that this be continued for four to six weeks, but Kehoe believes that deleading therapy is generally unnecessary. Another approach to the treatment of lead poisoning is the administration of sodium citrate (12 Gm. daily) in order to produce a soluble, nonionized lead-citrate complex which will be nontoxic and rapidly excreted. BAL does not appear to be useful in lead poisoning.

**PREVENTION.** The prevention of lead poisoning depends primarily on adequate control and ventilation of industrial processes involving exposure to lead fumes or dust, or, in emergencies, on the use of adequate respirators. Lead poisoning in the home, particularly of children, can best be prevented by the avoidance of any opportunity for children to chew on toys, cribs, or window sills painted with lead pigment paints. Fortunately, the use of lead paint is now almost entirely confined to exterior applications. The public should be educated to the dangers involved in burning old battery casings, as many serious and even fatal cases of lead poisoning have resulted from this practice.

**Mercury Poisoning.** Mercury is an extremely toxic substance capable of producing both acute and chronic poisoning. Acute mercury poisoning usually occurs in the home as a result of the accidental or deliberate ingestion of bichloride of mercury ( $HgCl_2$ ), whereas chronic mercury poisoning more commonly occurs at work as a result of exposure to mercury vapor. Mercury is unique among metals in having sufficient vapor pressure at normal ambient temperatures to permit serious exposure from inhalation of its vapor. Industrial mercury poisoning is prone to occur among mercury refiners, gold and silver refiners using the amalgamation process, instrument makers, and laboratory workers. The fur and felt hat industry used to be a common source of mercury poisoning (the Mad Hatter of "Alice in Wonderland" ex-

hibited many symptoms of mercury poisoning!), but is now fairly well controlled. On the other hand, a considerable incidence of mercury poisoning arose during the recent war among workers engaged in making the new mercury-cadmium dry batteries.

**ACUTE MERCURY POISONING.** Acute mercury poisoning ensues rapidly after the ingestion of bichloride of mercury. It occasionally follows the use of mercury-containing douches or exposure to air saturated with mercury vapor. Mercury is rapidly absorbed from the stomach and widely distributed throughout the body after brief storage in the liver. It is excreted via the kidneys and large bowel.

**SYMPTOMS.** The symptoms of acute mercury poisoning ensue rapidly. They are referable to the organs involved in the absorption and excretion of mercury, where the greatest concentrations are reached. Severe epigastric pain, nausea, and vomiting occur early, usually within a few minutes of the ingestion of ionizable mercury salts. There is usually a metallic taste in the mouth. The vomitus may be bloody, and ulcerations in the mouth are frequent. Death may occur within 24 hours, in which case the principal finding at post mortem is a severe gastritis. If the patient survives, then evidences of renal failure develop, with oliguria, proteinuria, and the presence of red corpuscles and formed elements in the urine. Death from renal failure may occur, in which case marked cloudy swelling and necrosis of the renal tubular epithelium are encountered. Mercury also exerts a profound toxic effect on the large bowel, producing colitis and a profuse, watery, often bloody diarrhea. The involvement of the colon may persist for a week or more, and be the primary cause of death in patients dying after one or two weeks.

**DIAGNOSIS.** The diagnosis of acute mercury poisoning depends primarily on the classic signs and symptoms coupled with a history of ingestion of a mercury salt. It can be substantiated by the chemical or spectroscopic identification of mercury in the vomitus, urine, or stool. It is important that the diagnosis be established early, as the effectiveness of treatment varies with the duration of the poisoning.

**TREATMENT.** The treatment of acute mercury poisoning should be instituted as soon as possible. Egg white or milk may be given at home as a first-aid measure. The stomach should be lavaged

with copious amounts of fluid in order to prevent further absorption of mercury, following which a saline cathartic should be instilled via the stomach tube. Fluid balance should be maintained by the judicious use of intravenous fluids. The most valuable agent in the treatment of acute mercury poisoning is BAL (dimercaprol), which is a fairly specific antidote. It should be given as soon as possible after onset. An initial dose of 5 mg. per kg. of body weight is given intramuscularly, followed by 2.5 mg. per kg. in 1 to 2 hours. A third dose of 2.5 mg. should be given in 2 to 4 hours, and a fourth dose within 12 hours in severe cases. Two doses of 2.5 mg. per kg. should be given on the second day, and a single similar dose on the third.

**CHRONIC MERCURY POISONING.** Chronic mercury poisoning is generally industrial in origin, but is not infrequent among professional workers engaged in laboratory work.

**SYMPTOMS.** The symptoms of chronic mercury poisoning are insidious, varied, and vague. The commonest is stomatitis characterized by increased salivation, a metallic taste, gingivitis, and loosening of the teeth. There may also be anorexia, indigestion, and diarrhea. Some workers develop a definite muscular tremor, which generally is fine at first but becomes coarser as the condition progresses. The tremor is increased during activity and absent at rest. Mental aberrations may develop, characterized by a peculiar combination of excitability and shyness in the presence of strangers, mental depression and dullness, and, occasionally, active hallucinations. Workers who handle mercury salts may develop a severe erythematous desquamating dermatitis accompanied by punched-out, deep ulcers.

**TREATMENT.** No specific treatment for chronic mercury poisoning is necessary. Recovery will follow withdrawal from exposure, although the mental changes and tremor may persist for long periods. An adequate diet should be maintained.

**Zinc Poisoning.** Mild, transient poisoning follows the ingestion of food or drink heavily contaminated with zinc salts, or the inhalation of air containing freshly generated zinc oxide fumes. Ingested zinc results in a gastroenteritis characterized by nausea, vomiting, and diarrhea occurring promptly and lasting several hours. Inhalation of zinc oxide fumes results in a fairly characteristic reaction variously known as metal fume fever, "zinc shakes," "galvo," "brass chills," or

brass founder's ague. The syndrome is well known to welders of galvanized metal and to workers in brass foundries, as both of these trades involve the production of zinc oxide fumes. Several hours after the inhalation of the zinc oxide fumes there is a rise in body temperature, sometimes as high as 103° to 104° F., accompanied by a "grippy" feeling, sweetish taste, mild to moderate paroxysmal cough, and leukocytosis. The fever subsides in 6 or 8 hours, but the increase in leukocyte count persists for 12 to 24 hours. An attack of metal fume fever confers an immunity which lasts for 24 to 48 hours. The mechanism of the febrile reaction to zinc fume inhalation is not well understood, but is probably due to the presence of denatured proteins in the respiratory tract.

### BROMIDE POISONING

The depressant effect of bromides on the central nervous system has been recognized for approximately 100 years, and has led to the widespread, indiscriminate use of various bromide salts as sedative agents. When given by mouth, the bromide ion is readily absorbed, after which it rapidly replaces chloride in the extracellular fluid, as chlorides and bromides are excreted by the kidney approximately in proportion to their concentration in extracellular fluid. The replacement of chloride by bromide does not affect the function of most tissue, but leads to central nervous system depression. Proper doses of bromide produce sedation, especially of motor areas; but excessive administration may lead to marked lassitude, mental depression, and memory impairment. Larger doses may lead to motor incoordination, disorientation, and even delirium. Coma and finally death may follow, especially if additional bromides are given to control the delirium of an already present bromide intoxication.

**Symptoms.** The symptoms of bromide intoxication may be extremely difficult to recognize because of the previous existence of mental or emotional disturbances in most patients given bromides. The first evidence of bromism may be an apparent exaggeration of the patient's nervousness or instability. If the administration of bromides is continued or increased, in an effort to control the aggravated symptoms, delirium will supervene. The delirium of bromide intoxication is generally characterized by delusions, fear, visual and vestibular disturbances, and impairment of memory. Some patients receiving

bromides for long periods may develop an acne-form rash.

**Diagnosis.** The development of delirium or at least increased mental aberrations in any patient receiving bromides should lead one to suspect the diagnosis. Since bromides may be taken without the knowledge of the physician, however, the diagnosis may be obscure. Once suspected, the diagnosis can readily be confirmed by the determination of the blood or spinal fluid bromide content. Levels of 200 mg. of sodium bromide per 100 ml. of serum is a strong indication of bromide poisoning, although some patients may tolerate higher levels without apparent ill effect while others may become delirious at far lower levels.

**Treatment.** Once the diagnosis is established, treatment is easy. All bromide administration is stopped, and sodium chloride is administered in large doses (10 to 20 Gm. daily), with smaller doses for patients with cardiac or renal disease in order to avoid cardiac failure as a result of excessive sodium administration. Bromide will be excreted with chloride in the urine approximately in proportion to their concentration in serum, so promotion of a high chloride output also results in a relatively greater bromide output.

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## Section 2—Physical Agents

# 93

## Disorders Due to High Environmental Temperature

T. R. Harrison

Heat Cramps  
Heat Exhaustion  
Heat Pyrexia

The clinical syndromes resulting from excessive environmental temperature are of three types which are designated, respectively, as heat cramps, heat exhaustion, and heat pyrexia (heat stroke). These disorders are especially common during the first few days of a heat wave before acclimatization has occurred. After the adaptive process to stress has caused decline in the amount of sodium in the sweat, the disorders are less common and the need for administration of sodium chloride as a preventive measure is less urgent.

**Heat Cramps.** This disorder occurs in individuals who develop diminished osmolar concentration of body fluids because they sweat excessively and drink water copiously. It has been especially common in the past in stokers and miners. The chief symptom is pain which is due to spasms of skeletal muscles. The blood and urine display diminished concentration of sodium and chloride. The disorder may be prevented by the use of dilute sodium chloride solution, instead of water, for drinking purposes, or by the ingestion of sodium chloride. Treatment consists in the administration of isotonic or slightly hypertonic sodium chloride solution or of enteric coated tablets until the symptoms are relieved.

**Heat Exhaustion.** This is a common and usually mild disorder during excessively hot weather. It seems to be more common in women than in men, and is more likely to occur in persons who are not acclimatized to hot weather. The syndrome appears to be related either to vasomotor changes, with distributional shift of blood from visceral areas to the skin, or to slight decline in total extracellular fluid volume. The chief symptoms are lassitude and faintness, but actual syncope may occur. Sweating may be profuse and

the body temperature undergoes little or no change. Prevention consists of reduction of physical activity during excessively hot weather (and especially when the individual is unaccustomed to such weather), the use of electric fans, and the free ingestion of water and sodium chloride. The enteric coated tablets of sodium chloride are less apt to cause nausea but may be excreted by patients with diarrhea.

**Heat Pyrexia (Heat Stroke, Sunstroke).** This condition, while less common, is of great importance because of its gravity, and because of its curability provided treatment is instituted soon enough and is energetically pursued. The disorder is particularly common in aged, infirm, or alcoholic subjects. It likewise occurs frequently in those who, without gradual acclimatization, travel rapidly into excessively hot localities. It is especially common during the first few days of a "heat wave." Physical exertion is apparently a predisposing factor. The striking predominance of the disorder in males is probably referable to the difference in the habits of the two sexes, as regards exertion and alcoholic "sprees." The occurrence of the disorder is intimately related to humidity as well as temperature. Thus heat pyrexia may be encountered with environmental temperature as low as 32° C. (90° F.) when the humidity is high, but is very rare below temperatures of 38° C. (100° F.) in areas of low humidity.

The classic *manifestations* of heat pyrexia are a *rapidly mounting body temperature in the presence of a dry hot skin occurring in an individual exposed to an excessively high environmental temperature*. The temperature may reach excessive heights, values of 44° C. (112° F.) being seen occasionally. The patient, at first apathetic, becomes stuporous and then deeply comatose as the temperature rises. The skin remains hot and dry throughout, but striking and abrupt changes in

color may occur. The flushed appearance which is usually striking in the early stages may suddenly be replaced by a grayish pallor. Such a change indicates the onset of circulatory collapse and the imminence (or presence) of irreversible damage to vital structures. This alteration in the color of the skin is associated with other striking alterations in the clinical pattern. The circulatory state is initially that of increased cardiac output (full, bounding pulse, high pulse pressure, prominent visible arterial pulsations, exaggerated heart sounds). This state changes to that characteristic of peripheral circulatory failure (Chapter 14). Congestive heart failure may occur in patients suffering from preexisting cardiac disease, or in subjects treated with excessive amounts of fluid by the intravenous route.

Hyperpyrexia produces extensive parenchymal damage in the various organs. Petechial hemorrhages occur diffusely, and especially in the brain and in the skin. Patients surviving the disorder may display, for prolonged periods, clear indications of cerebral, cardiac, renal, or hepatic injury.

The *pathogenesis* of the disorder remains obscure. The visceral damage is clearly the result of the hyperthermia. The immediate cause of death is peripheral circulatory failure in most instances, but may be heart failure in the case of patients given too much intravenous fluid at too rapid rates. The sudden onset of peripheral circulatory failure is apparently due to the replacement of the initial circulatory adjustment, visceral constriction with cutaneous dilatation, by visceral dilatation with secondary cutaneous constriction. The decline in cutaneous blood flow now participates in the vicious cycle. The elevation of metabolism due to the hyperthermia causes further rise in temperature. The initial inability to lose heat by evaporation of sweat is now complicated by inability to lose heat by radiation to the surrounding air, because insufficient blood is flowing through the skin.

The rise in body temperature is clearly due to the cessation of sweating. The unsolved question involves the mechanism of the sudden cessation of sweating. Certain individuals with congenital or acquired disorders of sweat glands have marked impairment of the capacity to sweat and must avoid hot weather. Why other individuals with no known previous disorder of the sweating mechanism should suddenly lose the capacity to sweat remains a riddle.

The *diagnosis* of heat pyrexia is usually made readily. With the exception of intracranial disorders the condition is the only common cause of a temperature higher than 42° C. (108° F.) in an adult. It is the only common condition in which *the combination of a rising temperature and a hot dry skin* is seen. The only conditions likely to cause confusion are other causes of high body temperature, but in almost all of these the skin is either dry, cold, and pale (in the stage of rising temperature) or moist, warm, and flushed (in the stage of sustained or declining fever). It is a wise rule to consider all adult patients, observed during very hot weather with a temperature of 41° C. (106° F.) or more, to be suffering from this disorder unless another cause can be demonstrated immediately. It is far better to treat an occasional patient who does not have heat pyrexia, than to fail to institute immediate therapy when this condition is present.

The proper management of heat pyrexia depends upon the realization that *the damage done to vital structures by a given level of hyperthermia depends on the time factor*. In this respect the body tissues may be compared to an egg, in that a certain temperature for a certain time may produce irreversible (hard-boiled) alterations, while the same temperature for a shorter time may lead only to reversible (soft-boiled) alterations. During periods of excessively hot weather, all hospitals should keep a tub filled with water and ice. The moment a patient with a temperature of 40.5° C. (105° F.) or more, who also has warm and dry skin, enters the hospital, he should be immersed in this tub and given massage to promote vasodilatation and heat loss. After the rectal temperature reaches 38° C. (100° F.), the patient should be removed to a bed and the temperature measured every few minutes, wet sheets and a fan being employed if it tends to rise again, or warm blankets if it declines below the normal level. It has been shown, in controlled experiments on animals, that immersion in ice water is definitely superior to the evaporative management in terms of the all-important objective of producing rapid decline in body temperature, and there is strong evidence that the same conclusion is valid in patients.

When peripheral circulatory failure exists after the temperature has been reduced to a normal level, intravenous fluids are indicated, but with due consideration of the points that many of the

elderly patients with the disorder have diminished myocardial reserve, and that heat pyrexia has been shown to impair the functional integrity of the heart. When heart failure supervenes, as is occasionally the case, digitalis and the other procedures which are valuable in treating rapidly developing heart failure (Chapter 238) are indicated.

The prognosis is very grave in patients with heat stroke, but the immediate and rapid reduction of body temperature often saves lives which would otherwise be lost.

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## 94

### Pathologic Effects of Cold

C. P. Yaglou and A. R. Behnke

Physiologic Responses to Cold  
Injurious Temperatures  
Death by Cold  
Resuscitation of Chill Victims  
Cold in Relation to Disease

Cold was by far the most important disabling stress encountered by military personnel in World War II. There were 84,670 cases of frostbite in the British Army alone, and cold, as in the Napoleonic campaigns, at times disrupted and brought to a virtual standstill the German advances in Russia. Exposure to both wet and dry cold, not only of ground troops but also of aviators and survivors on life rafts, was responsible for tremendous morbidity and emphasized the importance of protective clothing and certain prophylactic measures, particularly with reference to care of the feet.

The striking differences between the rate of cooling in air and in water are shown by the following data. In water at 34° F., 60 minutes' exposure is often fatal, with terminal rectal temperatures of about 77° F. In air at the same temperature, exposure is tolerable for a period of at least four hours. An exposure in air at 21° F.

for 14 hours produces hypothermia comparable to 60 minutes at 34° F. in water.

**Physiologic Responses to Cold.** With heavy clothing and proper nutrition, temperatures as low as -50° F. are encountered for short periods in polar regions, in high-altitude flying, and in certain industries, with no apparent injury to healthy persons. The first defense of healthy persons against cold is peripheral vasoconstriction, especially in the extremities, with a marked fall of skin temperature but without much change in rectal temperature. Excessive heat loss by radiation, convection, and evaporation from the skin is thus prevented, at least temporarily.

The hands and feet appear to be body thermometers. The tolerance for cold at subfreezing temperatures depends to a large extent upon the degree of rapidity with which cooling of the hands and feet takes place. A skin temperature of the fingers of about 50° F. is the lower limit for the maintenance of a reasonable degree of manual dexterity. No discomfort is experienced until the skin temperature of fingers and toes falls to about 60° F. from a normal of 80° to 85° F., or

until the temperature of the shoulders, back, or legs drops below 80° F. from a normal of 90° to 95° F. Intermittent shivering then begins, with a cyclic rise and fall of heat production and sensation of warmth. If these responses are insufficient to maintain heat balance, continuous shivering sets in which may double or triple the normal resting metabolic rate.

If the exposure is not too severe, skin and rectal temperatures may eventually stabilize at some new low level that can be maintained for some time by shivering. Lung ventilation rate, arterial pressure, and pulse rate increase to keep pace with the O<sub>2</sub> consumption. The blood volume decreases, and the water leaving the blood may accumulate in tissue spaces, or may appear in diuresis.

Chemical heat regulation by stimulation of adrenals and thyroid does not seem to play an important role in humans. No significant increase in heat production appears in the early stages of adaptation without frank shivering. A small increase, averaging 7 per cent of the normal metabolic rate, was observed after exposures of 10 days or longer to a temperature of 59° F. Although the subjects were lightly clothed, they did not shiver at this temperature. Discomfort, cyanosis, and sleeplessness gradually diminished, but apprehension of cold did not disappear completely, even after two weeks of continuous exposure.

The warmest clothing made will not protect the wearer long in temperatures much below the freezing point, without exercise. The fingers and toes suffer more from cold than any other part of the body because they cannot be protected adequately without application of external heat. First they become painful, then numb, and finally frostbitten. Disappearance of pain is a warning sign of imminent danger. The critical skin temperature at which capillary wall damage and edema occur is between 35° and 45° F.

Strenuous physical exercise may raise the metabolic rate as much as 10 times the resting rate, and may even induce generalized sweating in temperatures as low as -50° F., but much exertion is too fatiguing and might result in freezing of sweat and death after exhaustion.

**Injurious Temperatures.** The minimal temperature of water in which nude men in the basal state can maintain body temperature at normal levels is about 32° to 33° C. In water colder than

this, heat production is increased by shivering. In moderately cold water (20° to 30° C.) tests on men with their bodies immersed up to the neck level showed that there is a strong tendency for the rectal temperature to become stabilized at 35° to 36° C., and prolonged survival is possible. In water colder than 20° C., man cannot easily produce sufficient heat to maintain thermal balance for long periods. Thus at 10° to 15° C., cooling proceeds rapidly toward temperature levels that cause serious functional impairment.

In hypersensitive persons, exposure to ordinary degrees of cold may produce immediate local or general reactions, such as asthma, hives, vascular spasm, vomiting, neuralgia, convulsions, or syncope, the latter apparently by a histamine-like effect on capillary dilatation with pooling of blood in the periphery. Many of these patients can be desensitized adequately by gradual exposure to cold or by subcutaneous injections of histamine.

**Death by Cold.** When thermal compensation becomes inadequate after prolonged shivering and fatigue, reflex and mental activities are seriously numbed and the sense of coldness is abolished; shivering ceases, the metabolic rate falls, respiration and pulse become shallow and irregular, body temperature drops, and the victim finally passes into unconsciousness which may end in death. The chance of survival is small when the rectal temperature falls below 80° F., although the heart might still be functioning. A cancer patient survived a rectal temperature as low as 74° F., after having been subjected to therapeutic hypothermia.

In arctic operations, fliers falling into cold water (41° to 50° F.) have died in less than 30 minutes, while, at a water temperature of 68° F., survival was possible for a period of several hours.

Large-scale chilling experiments were carried out by German physicians in Dachau concentration camps in the winter of 1942-43. Prisoners, submerged in water of 36° to 54° F., showed a gradual drop of rectal temperature to 96° F., followed by a much steeper fall to about 86° F., at which consciousness was lost. It took from 70 to 90 minutes to reach this critical body temperature. Death, ascribed to heart failure, occurred at rectal temperatures between 78° and 86° F., after exposures of 53 to 106 minutes.

In all subjects chilled in water, there was a

marked increase in blood viscosity and leukocyte count, a twofold increase in blood sugar, and a significant increase in red blood corpuscles and hemoglobin. Auricular fibrillation regularly occurred when the rectal temperature dropped to about 86° F. Autopsies showed marked dilatation of the right heart, and cerebral hemorrhage in victims whose neck and occiput were submerged along with the rest of the body.

**Resuscitation of Chill Victims.** The most effective treatment of Dachau prisoners who were chilled to unconsciousness was rapid rewarming in baths of 110° to 120° F. for about 10 minutes, or until the rectal temperature rose to 93° F. The patient was then dried with a towel and wrapped in warm blankets. Patients who were conscious when rescued preferred bath temperatures of 105° to 110° F., as water at 115° was painful to the skin and caused some burns. In no case were such hot baths injurious.

On the other hand, American experience with shipwreck survivors exposed to moderately low temperatures for periods long enough to produce much reduction in blood volume, has indicated that gradual warming is best for such patients. Too rapid warming was likely to produce sudden vasodilatation and cardiovascular collapse.

Gradual rewarming is also the preferred treatment for trench foot and immersion foot conditions produced by cold, dampness, and immobility. In the presence of hyperemia or edema, direct cooling with ice or by cold air has proved of great value in promoting absorption of exudate and in relieving pain.

**Cold in Relation to Disease.** Chilblains, trench foot, and frostbite are the only conditions known to be caused directly by cold.

It is important to realize that chilblains, immersion foot, or trench foot arises when the exposed parts of the body are subjected to temperatures between 26° and 50° F. True frostbite occurs at or below 26° F., the approximate freezing point of the skin. In contrast with immersion foot, it is associated with actual freezing of tissue to the extent that formation of ice crystals may occur.

More important than cold in itself are chilling drafts and sudden temperature changes which are believed to predispose to disease by lowering resistance to infection. Local chilling may produce neuralgia, muscular pain, coryza, sore throat, bronchitis, or pneumonia, and is known

to exert an unfavorable effect in the treatment of these diseases.

The condition of the heat-regulating system of the body is believed to play an important part in predisposition to respiratory and circulatory affections. Heavy work in cold and damp air is held to be particularly injurious, and is sometimes associated with congestion and inflammation of the kidneys through chilling of body surfaces, as shown by Nedzel.

The burden of keeping warm in cold climates falls upon metabolism, digestion, blood circulation, and kidneys, and indirectly upon the nervous system. Some investigators attach much importance to sudden changes of atmospheric temperature and barometric pressure, which are believed to lead to a variety of acute and degenerative diseases.

Although cold is blamed for causing much misery, it also has some blessings. Aside from the treatment of frostbite and immersion foot, it is now being used as an anesthetic in amputations, in the treatment of burns, and in the control of hemorrhage, pain, infection, and shock. Cold is the only shockless anesthetic known; it anesthetizes the entire protoplasm as well as the nerves. Its full possibilities in the therapeutic field remain to be explored.

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## Disorders Due to Alterations in Barometric Pressure

A. R. Behnke

Effects of Compression
Pathologic Conditions of Ears, Sinuses, and Teeth
Aeroötitis Media
Aerosinusitis
Aerodontalgia
Pulmonary Gases
Carbon Dioxide
Oxygen
Nitrogen
Expansion of Abdominal Gas
Altitude Anoxic Anoxia
Oxygen Inhalation for Prevention of Anoxia
Effects of Decompression
Decompression Sickness
Symptomatology, Bends
Chokes and the Shock Syndrome
Treatment of Decompression Sickness

### EFFECTS OF COMPRESSION

The theory that pressure changes (apart from disturbances in gaseous equilibriums) do not in themselves induce physiologic effects provided the pressure is equally distributed to all parts of the body, may be regarded as tenable. If oxygen pressure remains constant, metabolism is not affected by altitude changes. It is well known that blood and cerebrospinal fluid pressures are not altered by so much as a millimeter during rapid fluctuations of pressure over a range of many atmospheres. Any effects on cardiorespiratory function, for example, can be attributed to change in oxygen pressure or to the effect of the altered density of the respired gas.

### PATHOLOGIC CONDITIONS OF EARS, SINUSES, AND TEETH

**Aeroötitis Media.** Such remarkable tolerance to pressure does not hold if pressure is unequally distributed over the surface of the body—e.g., in fluctuating pressure boots. Differential pressures of the order of 50 to 100 mm. Hg (0.5 psi) are associated with vascular distention and pain. The most common symptom associated with compression in diving, or altitude descent, is pain in one or both ears when the auditory tubes are obstructed. In low- and high-pressure chambers, the incidence of severe aeroötitis media during the compression phase of exposure is 6 to 15 per cent, the higher incidence occurring during the

months when acute infection of the nasopharynx is highest. Some degree of aeroötitis may be observed in 33 per cent of individuals exposed.

After or during the breathing of oxygen, aeroötitis may develop during sleep. The reason for this is that the Eustachian tubes rarely open during sleep and, since the oxygen is absorbed more rapidly than the nitrogen diffuses, the pressure in the middle ear may fall fast enough to cause edema, venous hyperemia, and pain as a result of “cupping.”

The etiology of the pathologic changes observed during compression can also be ascribed to cupping action on tissues when the pressure in the middle ear is “negative” relative to tissue pressure. Vascular dilatation, rupture, and even hemorrhage may occur during elevation of barometric pressure.

The rate of compression is the most important factor governing degree of trauma. In high-pressure chambers and in diving, descent can be made at a rate equivalent to 100 feet per minute (45 psi). This is comparable to descents in the low-pressure chamber of 3,000 to 5,000 feet per minute. However, in commercial passenger aircraft the rate of descent is limited to 300 feet per minute, and the incidence of frank otitis media among passengers has been less than 0.5 per cent.

In the treatment of aeroötitis it should be emphasized that recovery takes place spontaneously. Special measures are contraindicated. Infection of the middle ear is no more common following pressure trauma, provided swimming is avoided, than it is in the unexposed general run of population. With respect to hearing following acute pressure trauma, the audiogram reflects temporarily diminished perception of sound over the whole frequency range. The rarity or absence of permanent deafness from pressure trauma is in contrast to the frequent impairment produced by gunfire.

The most promising measure to reduce the incidence of otitis media due to chronic obstruction is the application of radium to the posterior naso-

pharynx to bring about atrophy of obstructing lymphoid tissue.

**Aerosinusitis.** Involvement of the sinuses (usually the frontal, due to blockage of the frontonasal duct) occurs in 1 to 2 per cent of exposures to compression. The same type of injury to the lining membrane is produced as in the ear. The pain elicited is severe and rather sharply limited to the area involved. A mild form of pressure trauma is that brought about by the absorption of oxygen in occluded frontal sinuses during the course of acute nasopharyngeal infection which induces the familiar "vacuum" headache.

**Aerodontalgia.** A very interesting phenomenon is the dental pain elicited during test exposure in the high-pressure chamber, which has been described recently as occurring in 1 to 2 per cent of aviation personnel. The etiology of this pain has not been clarified by experimental work. It seems unlikely that it is due to any other cause than differential pressure, which implies the presence of free gas either in blood vessels or in extravascular pulp tissue introduced during dental treatment, or in some other manner. The dental pain sharply limited to specific teeth (excluding maxillary sinusitis) indicates that the pulp is diseased.

## PULMONARY GASES

**Carbon Dioxide.** One immediate effect of rapid compression is an increase in alveolar carbon dioxide pressure. Conversely, during rapid decompression, carbon dioxide pressure tends to fall. Prior to the establishment of equilibrium, the effect on the respiration in divers has been noted following rapid descent, and in the low-pressure chamber during rapid ascent. Aside from the initial changes, pulmonary ventilation is the same for a given degree of activity from ground level to barometric pressures equivalent to 35,000 feet altitude, provided sufficient oxygen is used.

Resistance to breathing is approximately inversely proportional to the square root of the density. At 4 atmospheres, resistance is approximately doubled; at 0.25 atmosphere (34,000 feet) resistance is halved. Healthy individuals are not aware of a change in the character of their breathing at 10 to 0.25 atmospheres unless valvular breathing apparatus is employed. Patients deriving benefit from inhalation of a mixture of 80 per cent helium and 20 per cent oxygen would

experience the same degree of lessened respiratory resistance at 18,000 feet.

**Oxygen.** Numerous tests on man have made possible a better definition of the limits of oxygen tolerance. At high pressures, there is a marked increase in oxygen toxicity brought about by exercise. The irritant level for prolonged inhalation of oxygen has been found to be the same for man as for lower animals—namely, about 60 per cent of 1 atmosphere (428 mm. Hg)—and 100 per cent oxygen appears to be toxic (substernal distress, nose and throat irritation) after a period of about 12 hours. No sharp limit can be set, however, since individuals vary markedly in their response to 100 per cent oxygen. The partial pressure is as important as the percentage—e.g., 100 per cent oxygen is not toxic at 380 mm. Hg (18,000 feet). In one experiment, 100 per cent oxygen produced some irritation at ground level after 4 hours, but was well tolerated when continued for 24 hours at 0.25 atmosphere (34,000 feet).

**Nitrogen.** The narcotic action of atmospheric nitrogen, which becomes apparent at pressures greater than 4 atmospheres (100 feet diving depth), induces psychomotor impairment and even loss of consciousness at pressures in excess of 10 atmospheres (300 feet diving depth). This phenomenon resembles in many ways the state of light anesthesia, and may be explained, at least in part, by the Myer-Overton hypothesis which relates effectiveness of anesthetics to the lipid-water solubility ratio. Helium, less soluble in lipids than nitrogen, minimizes the narcotic effect. In a recent simulated dive to 550 feet in which a helium-oxygen mixture was breathed, the diver remained in good condition throughout and subsequent to the period of the dive.

## EXPANSION OF ABDOMINAL GAS

In early experiments on the use of helium in diving, the mouthpiece used produced salivation, so that considerable amounts of gas were swallowed at bottom depth. When these men ascended rapidly, the expansion of the gas retained in the stomach by contracted pyloric and cardiac sphincter muscles was sufficiently great to bring about collapse. The impression that swallowed air or gas mixtures, rather than food (except melons, beans, and carbonated beverages), is the source of most abdominal gas has been confirmed by the subsequent studies of Blair and others

A great deal more work is necessary in this field. Consideration should be given to the possible inverse relationship between abdominal gas and intestinal function, and to the fact that even minor degrees of distention, in the range usually considered normal, impair gastric and intestinal motility.

### ALTITUDE ANOXIC ANOxia

The problem of anoxia, which was so troublesome in World War I, and about which reports of progressive physical and psychologic deterioration and fall in ceiling altitude were frequent, was handled fairly well during World War II. The need for oxygen economy by using "demand" breathing apparatus stimulated investigation of altitude performance with respect to anoxia.

Exposures at 10,000 feet for six hours daily, five to six days a week over a period of four to six weeks, have produced remarkably few real signs of deterioration, although Halstead has reported impairment in the dynamic visual field reflected by an inability to perceive peripheral targets which previously had been readily detected. At higher altitudes, the dimming of the brightness of the visual field is one of the most constant subjective manifestations of anoxia, and it is now recognized that the slightest degree of anoxia reduces ability to see at night.

An 85 per cent arterial saturation of hemoglobin is associated with some impairment in daylight flying and percentages below 80 (above 18,000 feet) are associated with appreciable handicap. Most men can tolerate an altitude of 18,000 feet for half an hour, but even though they may be conscious they will be in a befogged state, and collapse may ensue if they stay up much longer.

Of 7,798 men exposed to a simulated altitude of 18,000 feet for about 15 minutes, 6.5 per cent developed syncopal reactions. The clinical results, including the evidence of electroencephalogram, indicated that in 10 thoroughly studied cases a high percentage of the "fainters" had disorders of the central nervous system tending toward epilepsy. The hyperventilation and alkalosis rather than anoxia were suggested as eliciting the epileptoid trend. At some altitude indoctrination units, however, syncopal reactions at 18,000 feet were less than 1 per cent. There is good reason to believe that purely psychic in-

fluences contribute to the vasomotor phenomena and that these are no more a reaction to anoxia than similar phenomena which follow the insertion of a hypodermic needle.

**Oxygen Inhalation for Prevention of Anoxia.** Aviation personnel in the military services are thoroughly indoctrinated at training centers and in the field in the use of oxygen-breathing equipment.

Provision is made for the use of oxygen on (1) all flights above 10,000 feet; (2) all flights of more than four hours' duration between 8,000 and 10,000 feet; and (3) night flights from the ground level, or at least from an altitude of 5,000 feet.

Personnel flying aircraft not provided with oxygen equipment are admonished not to exceed 15,000 feet nor to continue longer than two hours above 10,000 feet except in emergency.

### EFFECTS OF DECOMPRESSION

**Decompression Sickness.** Rapid decompression of divers and compressed-air workers may give rise to the formation of bubbles in the blood stream and fatty tissues. Considerable experimental data indicate that intravascular bubbles elicit characteristic symptoms of pain (bends), asphyxia (choke), and paralysis. There are also recent experimental data which indicate that extravascular bubbles giving rise to abnormal tissue pressures may elicit the characteristic pain phenomena.

When aviation personnel are decompressed rapidly from the ground level to high altitudes, they also develop, with the possible exception of permanent paralysis, identical but usually less severe symptoms. Minor signs are pruritus and skin rash, prone to occur if the skin is chilled during decompression.

Intravascular bubbles have been observed at autopsy in divers and caisson workers. In altitude decompression, however, bubbles have not been observed in man, although sludge formation (pseudohemagglutination within the vessels) has been observed and roentgenographs have shown the presence of gas in joint spaces and in tissues. Some experienced clinicians attribute the symptomatology of decompression sickness entirely to extravascular bubbles. The basic problem is whether or not intravascular or extravascular bubbles are primarily responsible for the symptoms.

**Symptomatology. Bends.** The most common manifestation is a dull, throbbing type of pain, gradual in onset, progressive and shifting in character, and frequently felt in the joints or deeply in muscles and bones. Pains of this nature are referred to as "bends," a term established by usage to denote a well-recognized clinical entity and used interchangeably with decompression sickness. Prior to the onset of pain there may be paresthesia, particularly in the joints, frequently described as numbness or merely an awareness that "something is not right." The skin temperature falls either prior to or during the period of pain, and the involved part becomes blanched in appearance. If the upper extremities are involved, there is likely to be a fall in temperature and decreased blood flow in the fingers.

Characteristic bone lesions in caisson workers support the view that the symptoms giving rise to bends originate, in part at least, from ischemic changes in bone. Lesions in the diaphyses and epiphyses of long bones, which are painless unless complicated by joint involvement, have been described, and are attributed to aseptic necrosis of bone or interference with nutrition occurring secondarily to the interruption of blood supply by liberated nitrogen.

A diver, following decompression, may remain in apparently good condition for several hours and then collapse because of paralysis of the lower extremities. Immediate and prolonged recompression usually brings about recovery, even following paraplegia of the lower extremities. Dogs rapidly decompressed from high pressures and then only partially recompressed (just sufficiently to prevent death from asphyxia) frequently develop paralysis of the hind legs, foot drop, a spastic type of gait, and paralysis of the bladder musculature. In both dog and man incompletely recompressed following massive embolism, residual symptoms may persist for months.

Although vertigo, deafness, occasional aphasia, and transient visual disturbances have been recorded, permanent impairment as a result of brain injury, in contrast with spinal cord lesions, is rare. Within the spinal cord itself the regions of relatively poor blood supply—i.e., the lower thoracic and upper lumbar—are most frequently involved.

Clinical conditions manifesting symptoms similar to those associated with the presence of air emboli in the spinal cord are tabes dorsalis and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries.

**Chokes and the Shock Syndrome.** The most interesting manifestation of decompression sickness is a type of asphyxia designated most aptly by the early caisson workers as "chokes." Normal breathing becomes shallow, rapid, and then dyspneic. Paroxysmal attacks of coughing, or true chokes, may precede loss of consciousness.

Untreated chokes with or without bends, in compressed air workers, are not infrequently attended by cold, moist skin, signs of impaired circulation, and hemoconcentration associated with surgical shock. Similar signs preceding collapse are observed occasionally in aviation personnel in pressure chambers either at altitudes above 35,000 feet or subsequently on return to ground level. The collapse is not the anoxic response which is sometimes observed at 18,000 feet when air is breathed, since recovery is delayed.

**Treatment of Decompression Sickness.** The objectives in treatment are immediate and prolonged recompression, and the judicious employment of oxygen and fluids. Such therapy has brought about recovery of divers seemingly in extremis. To treat the shock syndrome in aviation personnel, more pressure than that involved in descent to ground level may be required. The most frequent errors in treatment are:

1. Failure to give treatment to doubtful cases.
2. Delayed recompression. The longer treatment is postponed, the more pressure will have to be applied.
3. Failure to treat the serious cases adequately.
4. Failure to keep the "treated" patient near the chamber for a 24-hour period.

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## Radiation Injury

Shields Warren

Effects of Ionizing Radiation  
 Effects of Chronic Low-Level Radiation  
 Medical Effects of the Atomic Bomb

### EFFECTS OF IONIZING RADIATION

All living matter is continuously exposed to a minute amount of ionizing radiation derived from both cosmic radiation and the naturally radioactive materials in the soil and water. This constitutes the so-called background radiation, which is of such low intensity that it exerts no significant effect and rarely integrates to more than 20 r in a lifetime.

Exposure to significant amounts of radiation does not occur naturally. Radiation may be external, as from an x-ray tube, or internal, as from radium poisoning or the administration of radioisotopes, such as iodine<sub>131</sub>.

Since ionizing radiation cannot be detected by the senses, and since its effects are not immediately apparent, special precautions must be taken to protect against it when its presence is known or suspected. The chief means of monitoring are photographic film, electroscopes, or Geiger counters.

The "r" or roentgen is an arbitrary unit, based on ionization of air. The term "rep," roentgen equivalent physical, is used to designate the roentgen as determined by instrumentation, and is that quantity of ionizing radiation that undergoes an absorption in tissue of 83 ergs per gram. The term "rem," roentgen equivalent man, is used to designate the quantity of ionizing radiation which produces an effect in man equivalent to that produced by absorption of 1 roentgen of hard x-ray radiation.

Although there are four general types of ionizing radiation—alpha particles, beta particles, gamma rays, and neutrons—they vary greatly in their biologic effectiveness, the ionizing path of an alpha particle being many times as effective as that of a gamma ray, although its penetration is much less than that of the gamma ray. As a general rule, the more penetrating the radiation, the less is absorbed by any given unit of tissue

and hence the less the biologic effect. The response of tissue to injury by ionizing radiation does not vary with the type of radiation.

The mechanism of action of ionizing irradiation on protoplasm has not yet been sharply defined. That ion pairs are formed is clear, and that they may disrupt proteins and intracellular enzyme systems is also established. The formation of hydrogen peroxide within the tissues or the development of heat due to localized absorption of energy are among other hypotheses that have been put forward.

The effect of radiation depends to a considerable degree on the rate at which the radiation is given and on the volume of tissue irradiated. In general, microorganisms or relatively unorganized cells such as those growing in tissue culture are much more resistant to radiation than are more complex organisms.

Shorter-lived and hence more rapidly proliferating cells are generally rather more sensitive to radiation than are cells with little or no proliferative activity. Thus a granulocyte with a life of three or four days is far more sensitive than is a cortical pyramidal cell with a life approximately that of the individual in whom it occurs. Cells in mitosis are much more sensitive to irradiation injury than are resting cells.

Experience has shown that human somatic cells are not injured by radiation of low intensity. Only scattered data exist concerning effects on human germ cells, and animal experiments have not been conclusive. On this basis, the level of permissible occupational exposure has been set at 0.3 r per week, which provides a reasonable factor of safety. Changes in circulating lymphocytes can be brought about by doses as low as 15 r. Some degree of illness is almost constantly produced by a dose of 75 r delivered to the entire body.

The dose of external ionizing radiation, delivered within a short period of time, required to kill half a given human population is about 400 r. However, if the region of radiation is restricted to

a fraction of the body, as in the treatment of cancer, several times this dose can be given without appreciable systemic effect and with only localized destruction of cells.

The general principle of therapeutic irradiation of tumors rests on the fact that some types of tumors are made up of cells which are more responsive to radiation than normal cells and also that the tumor cells are more rapidly growing than are the corresponding normal cells of the body. Moreover, the changes induced in the supporting tissues by irradiation of a tumor include damage to blood vessels, with resultant impairment of nutrition, and increase in amount and density of collagen hampering the metabolic exchange of the tumor cells and also tending to obstruct their spread from the local site.

While in general the irradiation of localized tumor-bearing portions of the body can be accomplished without too serious harm to the rest of the body, there may be systemic reactions.

This so-called radiation sickness is probably related to absorption of protein split-products from damaged tissues. It consists of mild to severe nausea, usually without significant organic change. If the field of irradiation includes a portion of the intestine, and the irradiation is heavy (5000 r or more), there will be some diarrhea due to the acute response of the intestinal mucosa, which may continue on to actual ulceration and scarring. There are usually no significant alterations in the various components of the body fluids during this sequence of events.

In sharp contrast to this, however, is the type of radiation sickness resulting from irradiation of the entire body in a short period of time. It is chiefly with this type of response to radiation that we are concerned from the standpoint of internal medicine. This acute radiation syndrome is quite different from the effects of chronic low-level irradiation. Four phases have been described, but are not constant: the acute onset, with malaise ranging up to prostration, usually lasting some hours; a phase of relative well-being lasting up to several days; a period of severe illness of varying duration; finally recovery or death. Fever may develop early and, particularly in the absence of infection, is an unfavorable sign.

In total body radiation the relative sensitivity of the different body tissues largely determines the clinical character of the response. If the radia-

tion is sufficiently overwhelming to damage most cells without regard to their relative susceptibility to injury, death usually occurs within a matter of hours or possibly days, with no distinctive symptoms or signs other than weakness and lassitude progressing to prostration accompanied by a marked leukopenia. More usually, however, the dose of radiation is not sufficiently great to be immediately lethal, so that there is opportunity for the varied sensitivity of the different systems of the body to become apparent.

Probably the most sensitive cells of the body are the lymphocytes. The erythroblasts and the precursors of the granulocytes are quite sensitive also, so that a leukopenia usually develops within 24 hours after exposure following a transient leukocytosis of 12,000 to 15,000 cells per cubic millimeter. The prominence and degree of the leukopenia are roughly proportionate to the degree of exposure and hence are of some prognostic value. If the white cell count falls below 2000 per cubic millimeter within the first few days following exposure, recovery is unlikely. Owing to the longer life of the red blood corpuscles, anemia develops more slowly, but may be severe.

Hemorrhagic manifestations referable to the combined effect of thrombocytopenia induced by the radiation, increased capillary permeability from damage to the endothelial cells, and alterations in the coagulability of the blood probably largely mediated through hepatic damage, and in which a heparin-like substance is apparently involved, are of importance. In the survivors at Hiroshima and Nagasaki, the hemorrhages from body orifices, petechiae, and ecchymoses reached their peak five to six weeks after the initial exposure. The symptoms and signs due to them are variable, depending on the location and extent of the hemorrhage.

A severe anemia, frequently accompanied by pancytopenia, develops after several weeks. This is not because of resistance of the erythropoietic tissue itself, which is highly sensitive, but rather because of the long life of the circulating erythrocytes which delays evidence of the damage to the parent tissue. The bone marrow during this stage may show aplasia or hypoplasia, in which case the outlook for ultimate recovery is not too good, or it may show hyperplasia with delayed maturation.

Regeneration may be effective and complete or it may be partial. In some instances there is ap-

parent failure of maturation, large numbers of young forms proliferating and even crowding the marrow for months afterward.

Not only is the leukopenia an evidence of serious damage to the body as a whole, but also its existence permits infection to become established. Multiple cutaneous abscesses, stomatitis, and cellulitis of the neck are among the more obvious developments. The pathogenic agents may be a wide variety of organisms, including those usually saprophytic. Bacteremia is a not infrequent complication.

The mucosa of the intestinal tract is relatively susceptible to radiation and is, of course, in constant contact with a wide variety of bacteria. As a result, ulceration of the intestinal tract occurs, and the severity of the ulceration usually determines the character of the signs and symptoms, which may range from slight diarrhea and vomiting to bloody diarrhea or, rarely, ileus with practical necrosis of much of the intestinal wall. The mucosa of the colon is somewhat more sensitive than that of the small intestine.

Radiation injury to the skin is rarely seen in total body radiation because, in those cases where a sufficient dose has been received to bring about characteristic cutaneous changes, death usually occurs before they have opportunity to develop. When present, ulceration and edema are severe. However, some degree of erythema or transient epilation may occur more often. Some of the Japanese exposed to the atomic bombs at Hiroshima and Nagasaki were epilated, but in none who survived was the epilation permanent.

Lymphoid tissue shows initial atrophy, but may regenerate completely.

The rate of healing of wounds or fractures is not significantly altered by radiation insufficient to impair the blood supply, although radiation tends to inhibit phosphatase activity.

Some fatal cases show atrophy of the adrenal cortex, but significant changes in other endocrine glands, aside from the hemorrhages incident to the hemorrhagic diathesis, have not been observed. The adrenal cortical atrophy may be partly related to the malnutrition resulting from the syndrome.

Transient sterility has been noted in the male, but permanent sterility is not expected, as the sterilizing dose for the testis is close to the lethal dose for man. In women, the sterilizing dose for the ovary is considerably more than the lethal

dose, so, although transient sterility may occur, permanent sterility would not be expected in survivors.

While it is possible that alterations in the germ plasm may occur in those who have recovered from the acute radiation syndrome, insufficient data exist to permit judgment. In the light of animal experiments, there exists a greater chance of mutations appearing in the offspring than in the case of unirradiated persons, perhaps on the order of one or two per 1000 births.

## THERAPY

Treatment of this condition is in its infancy. At present, the most satisfactory therapy consists in liberal whole-blood transfusions, the use of antibiotics to control infection, parenteral feeding including the amino acid complexes, and the alleviation of such local abnormalities as may develop in the course of the general process. Adrenal cortical preparations, various vitamins, and toluidine blue as an antiheparin agent have been suggested and may have some value.

## EFFECTS OF CHRONIC LOW-LEVEL RADIATION

With the knowledge of radiation available today, there is little exposure to chronic low-level radiation. However, it occurred in the past among radiologists or others occupationally exposed. Radium poisoning has also appeared in some of those persons who drank water containing radium for its supposed therapeutic value. The ingestion of radium in any form is now recognized as highly dangerous. Chronic low-level radiation may be expected to damage the bone marrow with anemia or pancytopenia not infrequently preceded by a period of moderate leukocytosis and relative lymphocytosis. There is both in man and in animals a predisposition of the irradiated tissue to the development of malignant tumors. In man, leukemia, osteogenic sarcoma, fibrosarcoma, and epidermoid carcinoma have been produced.

There is evidence from animal experiments that there is shortening of the life span, in which lowered resistance to infection seems to play a part.

As in the case of the acute radiation syndrome, genetic mutations may be induced by chronic exposure, but no satisfactory human data exist.

## MEDICAL EFFECTS OF THE ATOMIC BOMB

Since the possibility of atomic warfare makes it necessary that every physician be familiar with the general principles of injuries resulting from an atomic explosion, some mention will be made of blast and thermal injuries as well as those due to ionizing radiation, even though these are not strictly within the field of internal medicine.

The burst of an atomic bomb in air has been compared to an explosion of 20,000 tons of TNT which, in addition to the release of mechanical energy, releases an enormous amount of radiant energy, in the form of infrared, visible, ultraviolet, and x-ray radiation as well as a flux of neutrons. In an air burst, residual radiation from radioactive fission products of the bomb is not a major problem, as very little of the fission products reach the ground at the site of explosion but rather are swept up into the stratosphere where they are greatly dispersed and do not achieve a significant concentration when fall-out occurs.

In an underwater burst, on the other hand, as in the second Bikini test, residual ionizing radiation may be a very serious problem, as not only is there temporary radioactivity in the components of the water from the effects of the neutron flux but, in addition, the radioactive fission products are mixed in the column of water and cloud resulting from the explosion and are rained back upon whatever is beneath. However, air blast and thermal radiation are not significant.

In an air burst, secondary air blast injuries resulting from falling structures and flying debris are frequent and varied and range from severe crush to minor lacerations. On the basis of Japanese experience, crush injuries will predominate, with a high incidence of less significant but painful and disabling accidents from flying glass fragments. Primary air blast injuries may be largely discounted. Any person sufficiently close to the center of an atomic explosion in air to have received primary air blast injury would have received also a lethal dose of ionizing radiation and probably would be fatally burned in the bargain.

The burns received from the thermal energy liberated are of two types, flash burns and flame burns. Flash burns result from the direct heat of the bomb explosion itself. The burns are sharply demarcated and usually restricted to exposed

areas of the skin, varying in intensity from severe to slight, according to the distance from the point of explosion. In Nagasaki, some flash burns developed in persons up to two miles from the hypocenter. Flame burns are due to the fires incident to the explosion of the bomb, and are no different from those commonly encountered. Both these types of burns should be treated as would comparable burns from nonatomic sources.

The ionizing radiation received from the bomb burst is almost instantaneous in character, and a dose of 400 r over the total surface of the body is sufficient to cause death of about half the exposed population.

The first symptoms to appear are nausea and vomiting, shortly followed by diarrhea. Fever accompanies the more severe cases. Those receiving heavier doses of radiation (1200 r or above) will die within 1 to 30 days in spite of treatment.

In the cases that survive the first few days, signs and symptoms referable to effects upon the more sensitive tissues of the body will be more clearly defined. Phagedenic ulcers and septicemia may develop as a result of the destruction of white blood cells and their precursors. About this same time or up until six weeks later, hemorrhagic manifestations appear, due to damage to megakaryocytes, interference with the heparin-antiheparin balance of the blood, and increased capillary permeability.

In some of those surviving beyond six weeks, a gradually developing pancytopenia appears, which eventually leads to death. Bone marrow biopsy may show aplasia, or the marrow may be hyperplastic with impaired maturation.

The intestinal symptoms are caused by ulceration of the small as well as the large intestine. Some ulceration is due to radiation necrosis of the relatively sensitive mucosal cells, some to absence of granulocytes to control bacterial invaders from the intestinal contents.

So far as can be judged from the Japanese survivors at the present time, the great majority of those exposed who survive the acute stage will return to approximately normal.

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# 97

## Pulmonary Disorders Due to Inhalation of Noxious Agents

John S. Chapman

Silicosis  
 Asbestosis  
 Siderosis  
 Bagassosis  
 Beryllium Disease of the Lung  
 Aluminum Pneumoconiosis  
 Bissynosis  
 Cadmium Worker's Disease  
 Gases and Volatile Irritants

### SILICOSIS

By far the most common of the pneumonoconioses, silicosis is perhaps also the most dangerous and disabling. The basic requirement for the development of the disease is the presence of particles of silicon dioxide of such a size and such a concentration as to result in the deposition of considerable numbers in the lung. Careful studies indicate that respiration must contain a minimum of 10,000,000 particles of a diameter of 10  $\mu$ , or less, before silicosis may develop, and that considerably larger numbers are required before all contacts will be affected. The effect of silicon dioxide is chemical rather than physical, and the various silicates are incapable of producing disease. Certain other materials such as the dust of bituminous coal, possibly aluminum and other earthy dusts, may act as inhibiting agents.

The particles within the lung produce an early lymphocytic infiltration which is rapidly followed by fibrous tissue formation and later by extensive hyalinization in the form of nodules. Still later, if secondary infection supervenes, there may be conglomeration of the nodules in large fibronecrotic masses.

Three stages of silicosis, based upon chest films and known pathology, are recognized. In the

first there is only a slight increase in fibrosis throughout the lung, associated with some degree of prominence of the hilar shadows. The picture is not sufficiently advanced to be diagnostic roentgenographically, and the diagnosis can only be suspected. In the next stage numerous small nodular infiltrations appear and there is still further increase in the markings, with reticulation quite prominent. The third stage is marked by the formation of large hyalinized nodules, usually in the upper lobes, while the remainder of the lung fields takes on hyperlucency, manifested pathologically as extreme emphysema.

Given chest films, it is rarely possible to assert definitely that the disease at hand is silicosis until one establishes an occupational exposure to silicon dioxide. At the top of such a list would be mining (the mineral is unimportant; the quartz matrix is what is significant), sand-blasting, foundry work (especially in the core room), the prolonged use of polishing and cutting wheels composed of sandstone, and stone-cutting and polishing.

Probably up through stage II the patient has few if any complaints, so that the condition as disease is dependent upon the third stage, in which the patient complains of much cough, shortness of breath, expectoration, fever, and night sweats. Authorities differ, but the majority seem to believe that conglomerate nodules occur only when infection (suppuration, tuberculosis) has been superimposed.

Physical examination offers on inspection characteristic changes of emphysema, but large

areas of dullness over the upper lobes are encountered frequently, and one may discern either bronchial breath sounds or absent breath sounds over these conglomerate foci. Rales are usually wanting. Clubbing of the fingers is marked, and secondary polycythemia may be evident if cyanosis has been of considerable duration. As in emphysema, the heart sounds are heard with difficulty. Cor pulmonale may develop.

As soon as the disease is recognized, the patient should be removed from his environment if he is a young man, but men of advancing years who have taken a score of years to develop their disease, and in whom it is probably progressing but slowly, may be permitted to continue.

The development of tuberculosis is quite common among silicotic patients and, as stated above, is one of the most frequent causes for coalescence of the nodules, which marks the third stage. Once superimposed upon silicosis, tuberculosis is almost universally fatal, since the patient's dyspnea prevents any active collapse therapy, and since the badly damaged lungs are but slightly resistant to dissemination.

### ASBESTOSIS

This is in effect merely a specialized form of silicosis. The disease is encountered in workmen who have been heavily exposed to atmospheres containing great amounts of asbestos fiber. The physical and roentgenographic findings, clinical course, and outcome are essentially the same as in silicosis. The distinctive feature is the expectoration of brownish, formed-elements of mucus, which on microscopic examination can be seen to contain fibers and spicules which are characteristic. Certain recent findings suggest that the disease may be associated with a considerably higher incidence of carcinoma of the bronchus than is to be found in the general population.

### SIDEROSIS

Siderosis is the deposition of extrinsic iron within the lung, and is to be distinguished from intrinsic hemosiderosis. When the condition was first described, it was thought that the main source of such deposit was electric arc welding and that ionic iron particles were requisite for the reaction. More recently, the condition has been discovered in acetylene welders also, so that it would appear that very fine particles of iron oxide may also be a factor. The condition pro-

duces no symptoms, results in no progression, and requires no treatment. The chest film reveals rounded nodules (2 to 3 mm.) usually located in the midlung zones or, according to some, a diffuse reticular fibrosis.

### BAGASSOSIS

This disease is the result of the inhalation of bagasse dust, bagasse being the name for the pulverized and dried stalks of sugar cane. As such, the disease is discoverable only in areas of sugar manufacture and in plants where bagasse is manufactured into insulating board. It is a subacute febrile disease marked by the formation of large, conglomerate shadows in the lung fields, a fever that persists for as much as two to three months, together with an outcome usually favorable both in regard to clinical symptoms and clearing of the chest film. No treatment has any effect on the course of the disease.

### BERYLLIUM DISEASE OF THE LUNG

This recently described disease is encountered among workers in the manufacture of fluorescent lamps, and among their families who are contaminated by the workers' clothing. Like others of this general type, this pneumonoconiosis frequently continues to develop for varying periods after the workman has left the dangerous environment. Most of the cases so far reported have occurred in women, but it is not clear whether or not this sex preference is real. The chest film in the first stage is stated to have a finely granular, "sandpaper" appearance, in the second to develop an overlying reticulation, and in the third to present true nodulation (1 to 5 mm.). Reports indicate that the disease has a high mortality.

### ALUMINUM PNEUMONOCONIOSIS

A condition apparently first described in employees of smelters dealing with bauxite, this disease produces as its significant manifestation intense dyspnea which eventually leads to death. An exposure of some years, however, appears to be requisite to the development of the disease. Roentgenographically, its recognition is said to depend upon the combination of marked irregularity of the diaphragms, widening of the mediastinal shadows and almost total loss of normal lung markings. Experimentally, it has been shown that aluminum particles are deposited in

the lung in long, needle-like crystals, and there excite a hyalinizing granuloma.

### BISSYNOSIS

This disease originally ascribed to the inhalation of cotton fibers and familiar to workers under such names as "gin fever," "Monday morning fever," etc., is now thought to be due to the inhalation of *Aerobacter cloacae*, which has been found frequently in stained, old cotton. But a few hours' exposure is sufficient to result in the infection, which has an abrupt onset with fever, chilliness, cough, retrosternal pain, and marked malaise. The chest film reveals one or more areas of patchy pneumonia. The condition is benign and runs its course within a few days at the most.

### CADMIUM WORKER'S DISEASE

Cadmium oxide at high temperatures is a highly lethal substance. Inhalation of its fumes, if they are present in any significant concentration, is followed by a sense of dryness in the throat, and in turn by a feeling of constriction of the chest, dry cough, and extreme dyspnea and cyanosis. Physical findings are essentially normal, but the film reveals patchy irregular infiltrations scattered throughout both lungs. At autopsy these lesions are found to correspond with areas of edema and hyperemia, together with some interstitial pneumonia. All of these effects are said to be entirely chemical.

### GASES AND VOLATILE IRRITANTS

A part of the problem involved is discussed in the section on bronchitis and emphysema (Chapter 251). The immediate acute situation is that of intense bronchiolar and bronchial spasm associated with pulmonary edema and cyanosis. The treatment at this stage consists of positive pressure oxygen, avoidance of intravenous fluid, and the administration of bronchodilators and antibiotics. In some instances the chest film reveals what appears to be a miliary interstitial pneumonia. The late results, either emphysema or bronchiectasis, are treated according to the requirements of the individual.

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Part VI

## DISEASES DUE TO BIOLOGIC AGENTS

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## Care of Patients with Febrile Illnesses

Paul B. Beeson

Rest in Bed  
Nursing Care  
Diet  
Fluid Intake  
Care of the Bowels  
Measures to Diminish Fever  
Symptomatic Treatment

Physicians have at their disposal an increasing number of highly effective specific agents for the treatment of infectious diseases. As a consequence, there is a tendency to concentrate attention on specific therapy, sometimes to the neglect of general measures which are useful in any febrile illness. In cases where there is no specific treatment, skillful general care may be the deciding factor. The present chapter deals with these matters, which have to be considered in the management of every febrile illness; they will not be repeated in the sections on specific infectious diseases.

**Rest in Bed.** Clinical experience has demonstrated beyond question that patients with febrile illnesses are usually benefited by bed rest. The work of the heart, kidneys, and liver is reduced, counteracting to some extent the acceleration of metabolic processes which accompanies fever. The recumbent position lessens malaise and relieves the sense of fatigue. Blood flow to the kidneys and liver tends to be greater in the recumbent than in the erect position, whereas the upright position favors congestion in these organs by increasing the venous pressure. These factors may be of importance in the outcome of nephritis or hepatitis. It has also been postulated that the recumbent position assists in the healing of pulmonary tuberculosis by increasing the blood supply to the upper parts of the lungs.

It should be noted, however, that bed rest has disadvantages. Diminished respiratory excursion may lead to atelectasis. Sluggish blood flow in the lower extremities predisposes to phlebo-thrombosis, a particularly serious threat in elderly patients. Even in normal persons, confine-

ment in bed for more than a day or two produces a noticeable diminution in muscular strength. Autonomic vascular reflexes do not act efficiently after bed rest, so that there is a tendency to orthostatic hypotension with giddiness or syncope. Furthermore, prolonged confinement may have an unfavorable psychologic effect on the patient. Although advisable and even necessary during the febrile stage of an illness, bed rest may actually be deleterious if prolonged unnecessarily.

Resumption of activity after a period of bed rest has to be gradual, especially in the case of the elderly patient. Initially he should be encouraged to move, turn, and sit up in bed. He can then be permitted to sit in a chair for 15 to 30 minutes at first, and for increasing periods thereafter. It is desirable that the patient take a few steps each time he is out of bed, since merely being lifted into a chair is of little real help in regaining strength. Activity should be increased as rapidly as warranted by the patient's age, previous health, and the duration of the illness.

**Nursing Care.** Since the fluid requirement is increased during fever, the nurse must give constant attention to administration of the types and quantities of fluids ordered. In prolonged febrile illnesses, maintenance of nutrition is of great importance; the nurse can help by urging the patient to eat, by feeding him if necessary, and by catering to his poor appetite. In seriously ill patients, dryness of the mouth may be a problem. Crusts, composed of inspissated mucus and epithelial cells, form on the lips, teeth, and tongue. Mouth washes help to get rid of these, or, if the patient cannot use mouth washes, the oral cavity should be cleansed frequently with gauze pledges moistened with water or with lemon juice and glycerin. Patients with fever may have profuse sweats; this calls for frequent changes of bedding and night clothes. Persons who are very weak should be turned from side to side at fre-

quent intervals, and should also be encouraged to take a few deep breaths frequently to prevent atelectasis. Inability to move about may also favor the occurrence of decubitus ulcers. These can nearly always be prevented by frequent turning, by keeping the sheets dry and free of wrinkles, by alcohol rubs, and by protecting the sacrum and other pressure areas with rubber rings. It is worth remembering that rubbing alcohol occasionally causes a dermatitis characterized by redness and scaling, with itching. For dry skins, baby oil is preferable. To prevent phlebothrombosis, the patient should be taught to exercise his lower extremities at least every hour while awake. Patients who have painful extremities should be protected against development of contractures as a result of disuse. They should move all joints, either actively or passively, through the whole range of motion each day. If this does not suffice, application of splints is indicated. Foot drop can be prevented by loosening the bedclothes at the bottom of the bed, or by use of a footboard.

**Diet.** Because of the accelerated metabolism and lack of appetite in fever, rapid weight loss is liable to occur, unless measures are taken to insure a high caloric intake. In prolonged febrile illness 3000 to 4000 calories per day will be needed. At the onset of acute infections there is a phase of negative nitrogen balance, lasting several days to weeks (see Chapter 33). This seldom can be counterbalanced entirely since most of the nitrogen administered during this period is immediately excreted. The giving of blood or plasma to provide protein is not advisable, since neither is a rich source of utilizable protein, and there is risk of pyrogen reaction, transfusion reaction, or transmission of homologous serum hepatitis. Nitrogen wastage can be kept at a minimum by supplying adequate calories in the form of carbohydrates and fats. Vitamin requirements, especially of the B group, are usually increased during fever, and vitamin supplements are advisable in prolonged illnesses. The utilization of vitamins is greater when they are administered orally in divided doses than when the same quantity is given in one parenteral injection. There are several satisfactory commercial multiple-vitamin preparations which may be employed.

As far as possible the caloric requirement should be supplied by way of the gastrointestinal tract, since it is almost impossible to administer the total caloric need by parenteral routes. For

example, intravenous injection of 1000 ml. of 5 per cent dextrose solution furnishes only 200 calories.

Because the appetite is poor, it is especially important to note the patient's preferences. As a general rule, he can be allowed any food for which he expresses a desire. There is little basis for the practice of restricting the diet in febrile illnesses to "soft" foods such as custard, junket, ice cream, puréed vegetables, etc. Their main justification lies in the fact that many of them are rich in carbohydrate and hence have some protein-sparing action. If the patient would relish such things as crisp bacon or other forms of meat, he can be allowed to have them.

**Fluid Intake.** During fever there is increased loss of water, by surface evaporation and by sweating. Persons whose temperatures are above 102° F. need at least 3000 cc. of water per day; the requirement is even greater if there is vomiting or diarrhea (see Chapter 28). Fluids by the oral route are often preferable to intravenous or subcutaneous injections, a fact which is sometimes forgotten. Since there is also need for calories, vitamins, and electrolytes, fluid taken by mouth can serve as a vehicle for these. Instead of plain water the patient can be given fruit or vegetable juices, carbonated sweetened beverages, milk, eggnog, soup, etc. The common nursing practice of adding ice to most drinks seems inadvisable, because cold liquids are taken in small sips, and the air swallowed with them may contribute to abdominal distention.

**Care of the Bowels.** Constipation is a common problem in patients confined to bed. Adequate fluid intake is the first step in its prevention. If this does not suffice, mineral oil or milk of magnesia may be given. Mineral oil should be given at night to avoid interference with absorption of fat-soluble vitamins. If an enema is necessary, "soapsuds" or "water and glycerin" enema is preferable to tap water or normal saline enema, because the irritating effect of the former solutions stimulates contraction of the colon and makes their evacuation easier for the patient. Fecal impaction is likely to occur in elderly enfeebled patients; it may be manifested by constipation, or instead by frequent passage of small liquid movements. Manual removal may be necessary, but usually an impaction can be softened by giving mineral oil orally, or by use of a small oil retention enema. Gaseous abdomi-

nal distention tends to develop when there is a grunting type of respiration, as in patients with pleuritic pain. Measures to relieve the pleuritic pain (see Chapter 100) may therefore diminish the abdominal distention. Gas may be withdrawn from the stomach or small bowel through a stomach tube. Additional measures include use of a rectal tube and administration of 1 ml. of 1:4000 solution of neostigmine hydrobromide by subcutaneous injection at four-hour intervals. Oxygen inhalation also lessens gaseous abdominal distention. Application of hot stupes is an old remedy which is not very helpful.

**Measures to Diminish Fever.** In addition to specific therapy, the question often arises whether such measures as antipyretic drugs or sponging should be employed to reduce fever. Antipyretics have certain disadvantages. They tend to produce a fluctuating body temperature, with alternate sweating and chilly sensations which are often more unpleasant to the patient than sustained fever. A precipitous fall in temperature induced by antipyretics occasionally results in a shock-like state. Furthermore, the patient's temperature is an important gage of the effectiveness of specific therapeutic measures which will be obscured by antipyretics. Nevertheless, when the temperature is very high (i.e., above 105° F.), or when delirium is present, attempts should be made to reduce fever. Antipyretic drugs such as

acetylsalicylic acid (0.6 Gm.) or aminopyrine (0.3 Gm.) may be given, and repeated every few hours in an attempt to hold the temperature at a lower level. Body temperature may also be reduced by sponging, with alcohol or with tepid water. When done skillfully, sponging often affords considerable symptomatic relief, and may be repeated every hour or two during a critical period of high fever, care being exercised to avoid fatiguing the patient. Sponging should be combined with gentle massage, to stimulate circulation of blood near the cooled surface of the body.

The management of very high fevers, such as occur in heat stroke, is considered in Chapter 93.

**Symptomatic Treatment.** Febrile illnesses are often accompanied by headache, photophobia, general malaise, and sleeplessness. Some of the drugs useful for headache and general malaise are also antipyretics, the disadvantages of which have already been mentioned. Codeine may be given, 30 to 60 mg., but this too may be undesirable because of its tendency to aggravate nausea or abdominal distention. The use of cold compresses or an ice bag for the headache, and sponging and alcohol rubbing for the general malaise may be of help. If photophobia is present the room should be darkened. For restlessness and insomnia, any of the commonly used sedatives, such as barbiturates, chloral hydrate, or paraldehyde, may be given.

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### Chemotherapy of Infection

Arthur P. Richardson and Paul B. Beeson

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Absorption, Distribution, and Disposition of Chemotherapeutic Agents  
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Sensitivity Tests  
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Effect of Chemotherapy on Bacterial Flora of the Body  
Sulfonamides and Sulfones  
Penicillin

Streptomycin  
Aureomycin  
"Chloromycten"  
Polymyxin  
Bacitracin

**Introduction.** The chemotherapy of infection may be defined as the use of drugs to suppress the growth of pathogenic microorganisms in the animal body. To be of practical value, a drug must exert its effect upon the parasite without

seriously damaging the cells of the host. It is remarkable that so many agents with this selective activity have been developed.

Although all living cells have much in common, functional differences exist by which they can be grouped in terms of vulnerability to certain compounds. Among the microorganisms, such groupings of species susceptible to chemotherapeutic agents are known as "antimicrobial spectrums." Some drugs have narrow spectrums and are highly restricted in their range of action, attacking only a few parasites. Quinine, for instance, is practically a pure specific for malaria plasmodia; indeed its action is limited chiefly to the trophozoite forms of these parasites. Other drugs, notably the newer antibiotics, have wide antimicrobial spectrums and inhibit microorganisms of many genera and species with very different biologic and pathogenic characteristics. With the discovery that urethane, aminopterin, and other compounds selectively damage certain cells in the mammalian body, the scope of chemotherapy has been broadened to include the attack upon malignant neoplastic cells, a field beyond the scope of this chapter.

Quinine, emetine, heavy metals, organic iodides, and other synthetic drugs are used extensively in treatment of protozoal and helminthic infections; information concerning them can be found in the chapters dealing with these specific diseases. The discussion to follow will be limited to two classes of chemotherapeutic agents active against bacteria: the sulfonamides and the antibiotics. The latter term is applied to substances produced by living organisms which interfere with the growth of other microorganisms. After isolation from natural sources, some of the antibiotics have been successfully duplicated by chemical synthesis.

So far as is known, all chemotherapeutic agents exert their effects in the intact animal by acting directly upon the parasite, and not by enhancing the natural defense mechanisms of the host. The principal action is a retarding of the rate of growth of bacteria (bacteriostasis) which enables the normal defense mechanism of phagocytosis, with or without the aid of antibody, to deal with them. When present in sufficient concentration, some drugs may also kill bacteria in vivo as well as in vitro.

**Mechanism of Action.** Despite extensive investigation, knowledge of the mechanisms of

action of the various chemotherapeutic agents is meager, and nothing more than hypothesis can be offered in explanation. The most plausible theory proposes that these agents in some way inhibit normal enzymatic processes in the parasites. This line of reasoning assumes either that disease-producing organisms are dependent upon enzyme systems different from those of the host cells, or that the metabolic processes inhibited, while vital to the parasite, are not immediately necessary to the life of the host. Since anabolism is more variable than catabolism, the anabolic phase is probably the one in which a chemotherapeutic agent can most effectively retard the parasite without harm to the host. The validity of this assumption is supported by many observations showing that both the sulfonamides and the antibiotics exert their effect during periods of rapid bacterial multiplication, and have no injurious effect on resting cells.

A reasonable concept of the action of chemotherapeutic agents is illustrated diagrammatically in figure 140. EM represents a complete en-

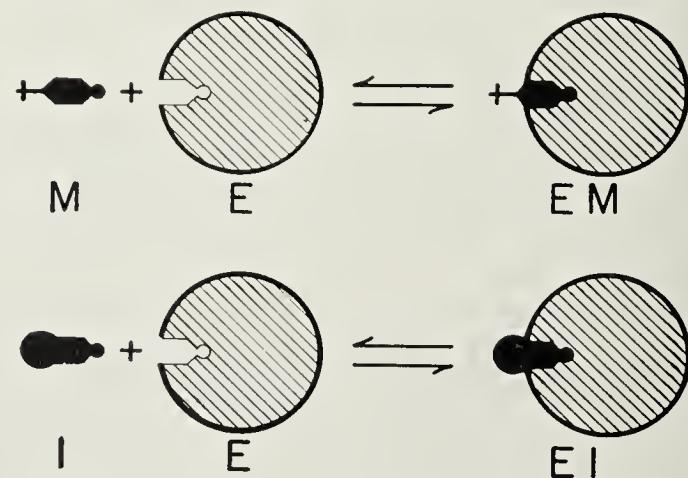


FIG. 140. Scheme of the possible mode of action of a chemotherapeutic agent (I) which acts as an analog of an essential metabolite (M). The chemotherapeutic agent is capable of uniting with an enzyme precursor or proenzyme (E), but the final product (EI) cannot carry out the function of the normal product (EM).

zyme capable of facilitating a metabolic process essential for growth of a microorganism. It is made up of two parts: M, an essential metabolite, and E, a partially formed enzyme structure, or proenzyme. These have physical and chemical properties which cause them to combine, forming the complete enzyme (EM). An equilibrium is established between their combination and dissociation. The chemotherapeutic agent (I) is a metabolic analog of the essential metabolite (M);

i.e., it possesses similar physical and chemical properties, and therefore competes with it for union with the proenzyme. Combination of the chemotherapeutic agent with the proenzyme forms an abnormal structure (EI), incapable of carrying out the function of the true enzyme in the parasitic cell. If the combination of drug and essential metabolite were a reversible process, successful treatment of an infectious disease would depend upon the continued presence of the drug in sufficient quantity to maintain a high proportion of inactive enzyme, thus hindering the growth of the parasitic cell. In terms of this hypothesis a sulfonamide would be the metabolic analog which interferes with utilization of para-aminobenzoic acid.

The nature of the biochemical interference caused by chemotherapeutic agents is incompletely worked out. As already mentioned, the sulfonamides may prevent the assimilation of para-aminobenzoic acid, which is normally incorporated in the formation of pteroylglutamic acid. Some evidence has been obtained indicating that both penicillin and streptomycin disturb the function of enzyme systems concerned with reactions of sulphydryl groups. Penicillin is known to block the utilization of glutamic acid by bacteria, and it also affects the dephosphorylation and depolymerization of ribonucleic acid, a process which normally supplies energy for protein synthesis.

**Absorption, Distribution, and Disposition of Chemotherapeutic Agents.** Successful chemotherapy of infection depends upon precise knowledge of the way in which a chemotherapeutic agent is handled in the body. Only with such information is it possible to achieve the optimal therapeutic effect with least injury to the host. The following examples will illustrate some of these differences in practical application of chemotherapeutic agents: In beginning therapy with sulfonamides, it is desirable to give a large dose initially to establish a certain concentration in various tissues; with antibiotics this is not necessary. Sulfadiazine rarely causes nausea when given orally, and is almost completely absorbed from the gastrointestinal tract; penicillin, while not causing nausea, is not efficiently absorbed from the gastrointestinal tract, necessitating much larger oral than parenteral doses. Penicillin can be given intramuscularly or intravenously without provoking troublesome local

irritation; aureomycin often induces nausea and vomiting, and parenteral injection is difficult because of the local irritating effect. The sulfonamides diffuse readily into all tissues, even penetrating to the spinal fluid in significant concentration; penicillin and streptomycin diffuse into the spinal fluid very poorly or not at all. Some chemotherapeutic agents become bound to body proteins after absorption, others remain free, while still others undergo chemical transformation. The renal clearance of penicillin is 500 to 1000 ml. per minute; of streptomycin, only 30 to 80 ml. per minute. Solutions of penicillin are relatively stable, whereas aureomycin deteriorates rapidly in solution, especially above pH 6.0. Sulfadiazine can cause severe renal injury, streptomycin has a specific toxic effect upon the eighth cranial nerve, and penicillin therapy may be followed by urticaria.

**Continuous Versus Intermittent Administration of Chemotherapeutic Agents.** The question is often raised whether a drug should be administered more or less continuously, in order to maintain a nearly constant level in the body fluids, or whether equally good or better results might be obtained by infrequent administration and fluctuating blood levels. It appears that no general answer can be given to this question; each drug and each disease must be considered separately. In some instances, as with streptomycin, results are satisfactory if the drug is given in large single doses at infrequent intervals, whereas in other cases, as with the sulfonamides, it seems necessary to maintain a relatively uniform concentration of the drug in the tissues. These differences can be interpreted in terms of the theory of mechanism of action which has already been described. For some agents one may visualize a situation in which the combination of drug and proenzyme is rapid, and in which the product formed is not readily dissociated. The amount of proenzyme inactivated would be determined largely by the peak concentration of the chemotherapeutic agent even if maintained for only a short time. In this circumstance the best result might be obtained by giving the total daily quantity in two or three doses, thus achieving high peaks of tissue concentration. At the other extreme would be a condition in which the drug-enzyme combination is easily dissociated; this would necessitate a significant concentration of drug in the tissues at

all times, in order to maintain its interference with the enzyme formation. Such a drug would be most effective if administered continuously, or at frequent intervals.

**Natural and Acquired Resistance of Bacteria to Chemotherapeutic Agents:** NATURAL RESISTANCE. Each chemotherapeutic agent has a certain range of effectiveness among the various classes of microorganisms. Presumably the principal determining factor in this is whether the enzyme system affected by the drug is essential to the existence of a given parasite. Another factor is the elaboration by the parasites of substances which inactivate the chemotherapeutic agent. For example, the *Pseudomonas* group of bacteria, which are naturally resistant to penicillin, produce a penicillinase which, when added to a culture medium, will inhibit the bacteriostatic action of that drug for bacteria normally susceptible to it. Some naturally resistant strains of *Staphylococcus* also have been found to produce a penicillinase. Certain bacteria whose growth is not inhibited by sulfonamides produce comparatively large amounts of para-aminobenzoic acid. Natural resistance to a drug, then, may be due either to lack of dependence on the enzyme system affected, or to ability to elaborate a substance which destroys the drug or antagonizes its action.

ACQUIRED RESISTANCE. Bacteria growing in the presence of chemotherapeutic agents may exhibit a change in susceptibility, by virtue of which they become able to grow in concentrations of drug which originally would have suppressed them completely. This kind of change can occur within the animal body as well as in the test tube. The rapidity with which it develops varies with different bacterial strains and with different chemotherapeutic agents. Streptomycin is notorious for inducing resistance; cultures of bacteria originally inhibited by a concentration of 4 micrograms per ml. can change within a few days so that they flourish in 5000 micrograms per ml. Of special theoretic interest is the emergence of a state of *dependence upon streptomycin* as a growth factor. In these instances the status of the drug seems to have changed from an antibacterial agent to a bacterial vitamin! This phenomenon has been observed with coliform bacteria, gonococci, and tubercle bacilli.

The development of drug resistance appears to

be the result of selective survival of naturally occurring variants in a culture. The presence of the chemotherapeutic agent does not increase the rate of appearance of these resistant forms, which are at first in such a minority that they escape detection. However, as the growth of susceptible organisms is inhibited, the resistant variants multiply and eventually outnumber the susceptible organisms. It should be emphasized that the occurrence of organisms resistant to the effect of an agent is not dependent upon the agent's presence. However, only when the more numerous susceptible forms are eliminated by the agent can the resistant forms multiply to such an extent that they predominate.

The acquisition of drug resistance is observed most frequently with streptomycin. With the sulfonamides and penicillin it occurs only occasionally, and is always a gradual process, requiring many subcultures in drug-containing mediums. There is little tendency for bacteria to develop resistance to aureomycin or "Chloromycetin." Acquired resistance to sulfonamides and penicillin is usually retained as a permanent characteristic long after the drug has been removed from the medium. Streptomycin resistance, on the contrary, is likely to diminish after withdrawal of the drug.

**Determination of Drug Concentration in Body Fluids.** As has already been indicated, knowledge of the absorption, distribution, and excretion of chemotherapeutic agents is of the greatest importance in determining methods of clinical usage. Sulfonamide and "Chloromycetin" concentrations in various body fluids can be determined chemically, using colorimetric technics. For most of the antibiotics, however, there is no means of chemical analysis, and the much more tedious and inaccurate bio-assay methods are required. The general plan of bio-assay technics is to test the body fluid (blood, urine, spinal fluid, etc.) for capacity to inhibit growth of a standard test bacterium, as compared with the effect of known concentrations of the chemotherapeutic agent. Two general methods are employed: (1) Test tube method: Successive dilutions of the body fluid are added to a series of test tube cultures of the standard test organism, and their growth-inhibiting effect compared with that of known drug concentrations. (2) Agar plate method: An agar medium is seeded with the test organism. The fluid to be tested and

known quantities of drug are then placed on the surface of the agar, either in small open cylinders or on saturated strips of paper; the concentration of drug in the body fluid can be estimated by comparing the zone of inhibition around the test solution with those around known concentrations of drug.

In clinical practice there is relatively little point in determining the concentration of antibiotics in body fluids because of the wide margin of error in bio-assay methods and because of the delay before the result is known. Blood levels are sometimes helpful during sulfonamide therapy, to warn the clinician when toxic levels are being approached.

such tests reliably. They are not necessary in all or even in a majority of cases; furthermore, there is only a rough correlation between clinical response to chemotherapy and the result of the sensitivity test. Nevertheless, the procedure may be invaluable in indicating which therapeutic agent to employ, and the general level of dosage required. For example, penicillin sensitivity tests on the causative organism should be done in all cases of bacterial endocarditis, and whenever a serious infection is not responding satisfactorily to treatment.

**Selection of Chemotherapeutic Agent.** In the therapy of infections the physician has to choose between an ever increasing number of effective

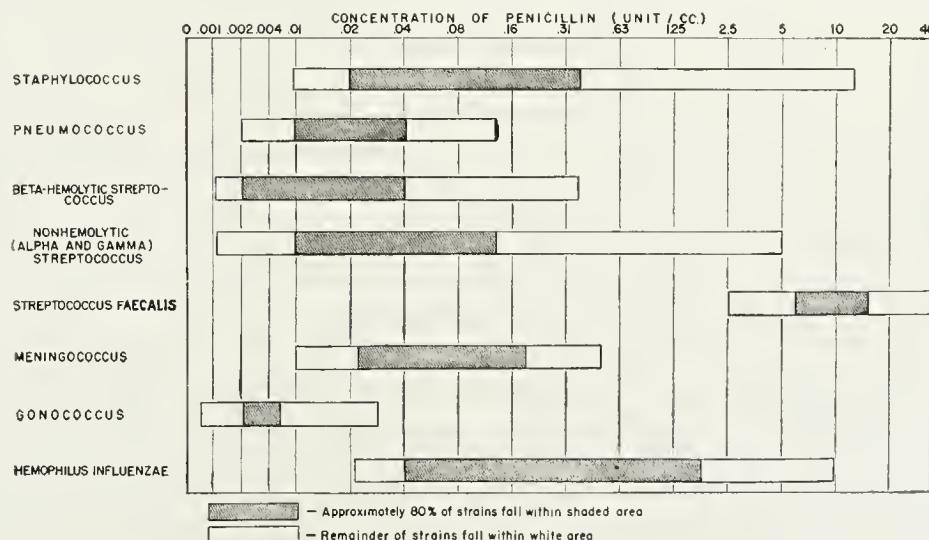


FIG. 141. Sensitivity of certain common pathogenic bacteria to penicillin.  
(Courtesy, Dowling: "The Acute Bacterial Diseases," Philadelphia, W. B. Saunders Co.)

**Sensitivity Tests.** The sensitivities of bacteria to various chemotherapeutic agents are usually determined by test tube technics. Culture mediums containing serial dilutions of the drug are inoculated with the organism to be tested and incubated. The "sensitivity" of the organism is expressed as the lowest concentration of drug which inhibits its growth. There is always some variation in susceptibility of different strains within a given species of organism. Figure 141 shows the ranges in sensitivity to penicillin of some common pathogenic bacteria. Variations of similar order occur in the sensitivities of Gram-negative pathogens to aureomycin, "Chloramycetin," and streptomycin.

Determinations of the sensitivity of an organism to chemotherapeutic agents may be helpful in the management of an infectious disease, and clinical laboratories should be able to carry out

antibacterial drugs. In order to obtain the best results, it is essential that he have a working knowledge of the common pathogenic microorganisms. While cultural studies are perhaps theoretically desirable in every case, this of course is not practicable. In many instances the etiology can be inferred from the clinical characteristics. Nevertheless, these are situations in which cultural studies are essential to proper treatment, and the conscientious physician must take whatever steps are required to obtain the help of a good bacteriology laboratory.

Even when the etiology of an infectious process is determined, selection of the appropriate drug does not follow automatically, because there may be wide variations in susceptibility among organisms of the same or related species. For example, in treating a series of *Proteus* infections it will be found that some strains respond only to

Table 88

APPROXIMATE ORDER OF PREFERENCE OF CHEMOTHERAPEUTIC AGENTS FOR VARIOUS PATHOGENIC MICROORGANISMS

Organism	Penicillin	Aureomycin	"Chloromycetin"	Streptomycin	Sulfonamides	Remarks
<i>Staphylococcus aureus</i>	1	2	0	4	3	
Beta-hemolytic streptococcus	1	3	0	0	2	
Alpha-hemolytic streptococcus	1	2	0	2	4	
<i>Streptococcus faecalis</i> (enterococcus)	2	1	0	*	0	* Enhances effect of penicillin
Anaerobic streptococcus	1	2	0	4	3	
Pneumococcus	1	3	0	0	2	
Meningococcus	2	2	?	0	1	
Gonococcus	1	2	2	0	2	
<i>Escherichia coli</i>	0	1	1	4	3	
<i>Proteus</i>	0	1	1	1	4	None reliable; marked variations between strains. In vitro—sensitivity tests helpful in making choice
<i>Pseudomonas (pyocyaneus)</i>	0	1	1	1	1	
<i>Klebsiella (Friedländer)</i>	0	1	1	1	4	
<i>Salmonella typhosa</i>	0	0*	1	0	0	* Some activity, but not comparable with "Chloromycetin"
Other Salmonellas	0	1*	1*	1*	1*	* Only occasionally effective
<i>Shigella</i>	0	?	?	2	1	
<i>Hemophilus influenzae</i>	0	2	?	1	3	Combined therapy advisable
<i>Hemophilus pertussis</i>	0	1	?	2	3	
<i>Brucella</i>	0	1	1	*	*	* Rarely effective alone, but have a "synergistic" action
<i>Pasteurella tularensis</i>	0	2	?	1	0	
<i>Pasteurella pestis</i>	0	?	?	1	2	
<i>Malleomyces mallei</i>	0	?	?	?	1	
<i>Malleomyces pseudomallei</i>	0	?	?	?	1	
<i>Bacteroides</i>	0	1	?	?	1	
<i>Bacillus anthracis</i>	1	?	0	2	3	
<i>Streptobacillus moniliformis</i>	1	?	?	0	0	
<i>Bartonella</i>	?	?	?	?	0	
<i>Corynebacterium diphtheriae</i>	1	?	0	0	0	
<i>Clostridium tetani</i>	1	?	0	0	0	
<i>Mycobacterium tuberculosis</i>	0	?	?	1	0	
<i>Mycobacterium leprae</i>	0	?	?	0	1*	* Promin or "Diasone"
<i>Treponema pallidum</i>	1	2	?	0	0	
<i>Leptospira</i> icterohaemorrhagiae	1	1	?	0	0	
<i>Spirillum minus</i>	1	?	?	0	0	
<i>Borrelia recurrentis</i>	3*	1*	1*	0	0	* Arsenicals may be superior to any of these
<i>Rickettsia prowazekii</i>	0	1	1	0	0	
<i>Rickettsia mooseri</i>	0	1	1	0	0	
<i>Rickettsia tsutsugamushi</i>	0	?	1	0	0	
<i>Rickettsia rickettsii</i>	0	1	1	0	0	
<i>Rickettsia burnetii</i>	0	1	1	0	0	

Numbers indicate approximate order of preference.

0 = Not effective.

? = Effectiveness not satisfactorily determined.