

PATHOLOGY
ANDERSON

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PATHOLOGY

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*With 1241 Illustrations
and 10 Color Plates*

SECOND EDITION



ST. LOUIS
THE C. V. MOSBY COMPANY
1953

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Reprinted
December, 1954

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

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PREFACE TO SECOND EDITION

In the second edition the original objectives in the production of a single volume text on pathology have been adhered to with but minor modifications. Although almost all parts have received some revision and have been brought up to date, certain subjects have been given greater emphasis and others have been shortened as seemed advisable for the sake of balance and according to the apparent importance of various diseases or disease processes. The unusual relative prominence given to the effects of radiation, tropical diseases, and diseases of the skin, special sense organs, skeletal system, and nervous system is continued. Many small additions have been made, which seem unnecessary to list. Many new illustrations have been added and old figures replaced. Most of the original contributors have again generously participated in this cooperative effort. They have been joined by others who have exhibited the same tolerant and helpful spirit in attempting to produce a balanced and unified presentation of a complex subject.

The first undergraduate course in pathology should be but the beginning and not the end of the study of this subject. The use of a book of this size and scope by the undergraduate medical student appears to be justified where the teacher of pathology executes his true functions of guidance, interpretation, stimulation, and encouragement. We should all be students of pathology throughout our lives as physicians, differing from our undergraduate colleagues only in the stage of our learning and experience. Those of us who, by chance of time and by virtue of experience, have progressed further along the road of knowledge should not underestimate the intelligence, capabilities, and needs of our less-advanced fellow students, even though they may be but beginners in the subject. A factual and orderly presentation of pathology should be of use to a beginner under the proper guidance of a teacher, as well as to a more advanced student. An attempt to provide a guide for the beginning student to the subjects of primary and lesser importance is found in the use of larger and smaller sizes of type. It is hoped that this book will continue to be a useful aid to the student of pathology, both during and after formal courses, and in correlation with other aspects or subjects of the clinical practice of medicine. Many of the subjects or conditions included, usually in smaller type, are designed to make the book useful as a reference tool for more advanced students, or for pathologists and other practicing physicians, although encyclopedic completeness is not implied.

The Editor is grateful to the many people who have taken the trouble to give constructive criticism and helpful suggestions orally and by letter. Although too numerous to mention individually, they also are contributors to this book and have played an important part in the revision. The Editor realizes that little of this book could have been accomplished alone, and that it is the product of the unselfish cooperation of the contributors, the publishers, and the Editor's assistants and co-workers. Miss Charlotte Skaeel, as my secretary and editorial assistant, has borne an increasingly significant share of the work in this revision. Her conscientious industry and unflagging interest have been most important in its accomplishment. Dr. Robert L. Kascht also gave generous assistance. Without the forbearance and encouragement of family, friends, and associates the task of revision would have been difficult indeed.

W. A. D. ANDERSON.

Miami.

PREFACE TO FIRST EDITION

Pathology should form the basis of every physician's thinking about his patients. The study of the nature of disease, which constitutes pathology in the broad sense, has many facets. Any science or technique which contributes to our knowledge of the nature and constitution of disease belongs in the broad realm of pathology. Different aspects of a disease may be stressed by the geneticist, the cytologist, the biochemist, the clinical diagnostician, etc., and it is the difficult function of the pathologist to attempt to bring about a synthesis, and to present disease in as whole or as true an aspect as can be done with present knowledge. Pathologists often have been accused, and sometimes justly, of stressing the morphologic changes in disease to the neglect of functional effects. Nevertheless, pathologic anatomy and histology remain as an essential foundation of knowledge about disease, without which basis the concepts of many diseases are easily distorted.

In this volume is brought together the specialized knowledge of a number of pathologists in particular aspects or fields of pathology. A time-tested order of presentation is maintained, both because it has been found logical and effective in teaching medical students and because it facilitates study and reference by graduates. While presented in an order and form to serve as a textbook, yet it is intended also to have sufficient comprehensiveness and completeness to be useful to the practicing or graduate physician. It is hoped that this book will be both a foundation and a useful tool for those who deal with the problems of disease.

For obvious reasons, the nature and effects of radiation have been given unusual relative prominence. The changing order of things, with increase of rapid, world-wide travel and communication, necessitates increased attention to certain viral, protozoal, parasitic, and other conditions often dismissed as "tropical," to bring them nearer their true relative importance. Also given more than usual attention are diseases of the skin, of the organs of special senses, of the nervous system, and of the skeletal system. These are fields which often have not been given sufficient consideration in accordance with their true relative importance among diseases.

The Editor is highly appreciative of the spirit of the various contributors to this book. They are busy people, who, at the sacrifice of other duties and of leisure, freely cooperated in its production, uncomplainingly tolerated delays and difficulties, and were understanding in their willingness to work together for the good of the book as a whole. Particular thanks are due the directors of the Army Institute of Pathology and the American Registry of Pathology, for making available many illustrations. Dr. G. L. Duff, Stratheona Professor of Pathology, McGill University, Dr. H. A. Edmondson, Department of Pathology of the University of Southern California School of Medicine, Dr. J. S. Hirschboeck, Dean, and Dr. Harry Beckman, Professor of Pharmacology, Marquette University School of Medicine, all generously gave advice and assistance with certain parts.

To the members of the Department of Pathology and Bacteriology at Marquette University, the Editor wishes to express gratitude, both for tolerance and for assistance. Especially valuable has been the help of Dr. R. S. Haukohl, Dr. J. F. Kuzma, Dr. S. B. Pessin, and Dr. H. Everett. A large burden was assumed by the Editor's secretaries, Miss Charlotte Skacel and Miss Ann Cassady. Miss Patricia Blakeslee also assisted at various stages and with the index. To all of these the Editor's thanks, and also to the many others who at some time assisted by helpful and kindly acts, or by words of encouragement or interest.

W. A. D. ANDERSON.

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PATHOLOGY

Chapter 1

INTRODUCTION

PAUL KLEMPERER

Pathology is that branch of natural science which is concerned with the search for the cause and mechanism of disease. In this general sense the term applies to disease of all living organisms. Human pathology is primarily concerned with disease in man but does not exclude the insight which is gained from the study of disease in animals and plants. Fundamental facts of morbid life are revealed by exact observation and purposeful experiments on animals and plants.

The everyday word "disease" is an abstraction, and abstractions obviously cannot be the immediate object of natural science, which is necessarily founded upon observation of natural phenomena. The concept of disease has been established by extracting and totaling those characteristics of the sick which differ from the norm. In our observation of the sick and the healthy we study manifestations of life, and life presents itself to our senses as form and action. These manifestations are investigated with methods involving precise measurement. Anatomy—gross and microscopic—is concerned with normal form. Physiology inquires into normal function. Life, however, is also experienced subjectively by the mind, and investigations of mind belong to the realm of psychology.

Sickness in the individual is recognized by manifestations of life which are different from those of normal life and are designated as symptoms. These evidences of disease are both subjective and objective. Subjective symptoms, such as pain, itching, nausea, discomfort, and emotional or intellectual disturbances, are of great importance in the recognition of ill-health but have not yet been subjected to the same qualitative and quantitative analysis which has been applied to objective symptoms. It has long been recognized, however, that subjective symptoms can and should be correlated with the outward manifestations of illness. The application of biochemistry and biophysics to the investigation of psychopathic persons and the study of mental disturbances in persons afflicted with obvious physical ailments illustrate the endeavor to align diseases of the mind with those of the body. The attempt to understand the mind at the level of somatic organization (or in terms of bodily function) must not be regarded as the only scientific approach to mental diseases. Man as a social animal cannot

be completely understood apart from his social environment, and the impact of the forces of society upon his mind require to be considered no less attentively than the influences exerted by chemical or physical factors upon his body.

Manifestations of disordered life which can be perceived by the senses constitute the objective symptoms of disease. From the earliest days of civilization, disease has been an object of intense interest to mankind. The medical records of the ancient Greeks are still a source of inspiration for us; their golden merits continue to shine in the light of modern science and exemplify the eternal value of accurate observation. Yet upon a mere perplexing multitude of symptoms and signs no lasting edifice of medicine can be erected. While the intuitive Hellenic genius recognized connections which modern medicine is scarcely beginning to understand, the Hippocratic system of pathology was doomed because it lacked the firm foundation of anatomy and rational physiology.* For more than a thousand years the progress of medicine was largely arrested. It began anew with the advancement of anatomy and physiology, but centuries had to pass until it was realized that the search for the intrinsic reason of disease must originate in observations of altered form and function of the living organism.

Having briefly outlined the purpose of pathology, we must now consider how investigations in pathology have proceeded and what they have accomplished. In pathology, as in all natural sciences, understanding must begin with observation and description. The earliest observations were concerned with obvious manifestations of abnormality of the patient during life—e.g., variations in the rate and quality of pulse or respiration, fever of varying type and intensity, abnormalities of excretion and secretion, and changes in bodily appearances and behavior. Empiricism, mingled with mysticism and vague philosophical theories of nature and man, led to the concept that disease was a living being which existed independently within the body of the patient. Numerous diagnostic terms, which are still in use today, such as cancer and lupus, are vestiges of this period.

*Genius is revealed in a delicate feeling which correctly foresees the laws of natural phenomena. But we must never forget that correctness of feeling and fertility of idea can be established and proved only by experiment (Claude Bernard).

Other terms, such as typhus and rheumatism (flowing pain), are derived from conspicuous objective or subjective symptoms of disease. These signs, however, are by no means the most important ones in the light of present knowledge.

The restrictions placed upon the cultural development of man during the centuries which followed the decline of the Roman Empire were finally lifted by the Renaissance. The revival of medicine was characterized by intense interest in the human body. Anatomic investigations were encouraged by enlightened rulers and the secrets of the fabric of the human body were rapidly revealed and divulged. These disclosures, coinciding with discoveries of universal laws of nature, stimulated inquiries into the mechanism of the human body. It is beyond the scope of this introductory chapter to depict even in rough outline the history of this natal period of modern medicine; yet the principles of pathology can never be fully understood without an appreciation of the labor of the creators.

Descriptive anatomy had established the norm of the structure of the human body. Superstitious fear of the dead had given way to the relentless curiosity which delved into the human body in an attempt to explain the mysteries of life. It was inevitable that medicine, challenged by the riddle of disease, should turn to anatomy for the answer. As structural alterations of organs were discovered, pathologic anatomy became established as a descriptive science and the symptoms of disease came to be correlated with the organic alterations revealed at autopsy. In 1761 the monumental work of Morgagni appeared; the anatomic conception entered the system of medicine and dominated it for nearly a century. It revolutionized medical diagnosis by providing a foundation to which the fluctuating symptoms of disease could be anchored. It now became the aim of scientific physicians to anticipate during the life of the patient the organic changes which would be disclosed at autopsy. Exact methods of physical examination, such as auscultation, percussion, and palpation, could be developed only after pathologic anatomy had disclosed the actual gross organic changes in disease. Not satisfied with these indirect methods of perception, ingenious investigators aimed at direct visualization of the organic alterations and invented instruments such as the laryngoscope and the cystoscope. X-ray diagnosis is likewise based largely upon the existence of physical changes in diseased organs. Thus the development of this important branch of medicine is founded upon the information supplied by pathologic anatomy.

For nearly a century Morgagni's idea of descriptive and correlative morbid anatomy held the lead in the progress of pathology. Yet, almost from the beginning of the era of pathologic anatomy, there were minds which challenged the primacy of a descriptive doctrine as the ultimate goal of pathology. They questioned the identification of disease with morbid alteration, and they ridiculed the overestimation of anatomic diagnosis as the final aim in the search for the nature of disease. It is the eternal con-

tribution of Rudolf Virchow to have recognized the inevitable sterility of a merely static appraisal of the structural alteration associated with disease. In prophetic articles as well as by means of original investigations in pathologic anatomy and histology he stated precisely the leading idea of pathology and produced a "regulative principle" (Royce) for future research. His dictum, "disease is life under altered conditions," is the master plan of a rational pathology. Life as form and function is the object of investigation—not form alone and not function alone. Altered life is under inquiry as it is seen at the sickbed, in the experimental animal, and in its final manifestation at the autopsy table. Each goal is approached by different methods; but the ultimate aim is integration into one science: pathologic physiology, the true science of medicine. This refers not to physiology in the narrow sense of the academic curriculum, but to physiology in its original sense, the proximate reason of the nature of man. Merely a century has passed since the first issue of his *Archiv*, in which Virchow originally announced his new doctrine. In the same year he formulated the principle which up to the present time has remained the axiom of research in pathology: to understand the inception and evolution of morbid states.

The pathologist concerned with the structural aspect of disease cannot confine himself to mere description. Pathologic anatomy originated as a branch of normal anatomy; it employed identical methods of gross and microscopic observation and description; but anatomic science advanced from mere description to an inquiry into the evolution of form. Morphology, concerned with the intrinsic reason of form, aims at an understanding of the formation and transformation of organic nature (Goethe: *Zur Botanik*, 1817). The concept of morphogenesis stimulated the development of embryology and comparative anatomy as components of normal anatomy. Pathologic anatomy utilizes the disclosures of these sciences in the interpretation of human monstrosities. Teratology and comparative pathologic anatomy have developed into an important field of biology; but beyond these special applications, the morphologic conception is a fundamental principle of pathologic investigation. Morphology rests upon the recognition that organic structure is constantly undergoing transformation. It is founded upon the comparison of different phases of organic life. Morphologic pathology compares normal with altered structure and correlates different states of pathologic lesions. It establishes relations between facts ascertained by observation, it correlates the morbid with the norm, and it teaches us that structural phenomena not only exist but that they pass through developmental stages. It introduces the dimension of time into the interpretation of static facts and it places them in the movement of life.

Life is manifested in structure and in function; the two cannot be dissociated. The maintenance of normal structure of living substance is guaranteed by the fundamental functions of assimilation and reproduction, and proper function is maintained by normal structure. This

holds true for life in its most primitive as well as in its highest organization. A morphologic approach to structure implies a correlation between form and function. Thus, morphologic pathology guides us in visualizing aberration of function and makes structural change intelligible in terms of process. It leads us to the realization that pathology must strive for an understanding of the mechanisms of disease. The complexity of the human body compels us to correlate structural and functional alterations at different levels of organization. Only on the plane of organs or complex tissues can changes of circulation and homeostasis become visually manifest, while alterations of metabolism and reproduction are revealed at the level of cells or intercellular substances.

While morphologic pathology is obviously dependent upon structural organization, it must always be remembered that living form is inseparably connected with matter (Needham). Biochemistry in its application to the analysis of organs and tissues is engaged in the search for the ultimate constitution of living matter without consideration of structure. Histochemistry, however, attempts to identify the chemical nature of morphologically separable units of cells and tissues. On the one hand, histochemistry employs the principle of anatomy—to separate separable things (Bensley). In addition to conventional histologic technique it utilizes the most refined methods of separation, such as microdissection, ultracentrifugation, and electronic microscopy. On the other hand, it adapts certain methods of analytic and enzyme chemistry and of physics, such as ultrascopscopy and x-ray diffraction, to the investigation of cells and intracellular substances. A combination of such methods has already promoted research in histology, embryology, cytology, and genetics. The pathologist concerned with the structural aspect of disease must realize that a fuller understanding of life, normal and abnormal, will only be achieved by recognition of the chemical and physical constitution of the living substance and its regulation by the laws disclosed by natural science. Such recognition ties morphologic pathology to biochemistry, biophysics, and to biology in general. Thus the pathologist must keep abreast of every advance in these sciences.

Biology, as a science concerned with the manifestations of life, investigates also the conditions under which normal life is maintained in form and function. The living organism can scarcely be imagined outside of its natural environment but should be viewed as a part of the universe. Biologic sciences also must include in the scope of their inquiry the forces of the environment and mechanisms by which the living organism is adapted to their influence; they must attempt to interpret phenomena of life as a result of interaction between the forces of the organism and those of the external environment. Pathology, conceiving of disease as life under altered conditions, tries to understand life in terms of a change in this interaction. Complex external and internal factors determine disease. It is the final object of pathology to recognize all fundamental factors

in their action and interaction, in order to investigate causality in disease. Exact observation and correct correlation lead to inferences of causality which must be tested by experiment. The recognition of external factors as causes of disease does not complete the search. Oertel clearly states: "Any perfect causal explanation must include the complete and connected chain of all events which are responsible for phenomena, and these, moreover, must be in their proper position." In other words, etiology is not synonymous with pathogenesis. We must realize that the search for causality in disease must not stop with the recognition of external cause but must progress to demonstrate the mechanism by which the cause acts. Pathologists cannot rest merely with the reproduction of phenomena of disease by experiment; they must strive to "dissociate all the complex phenomena successively into more and more simple phenomena" (Claude Bernard). Only if we recognize the elementary principles of the causative factors and their action upon the animal and human body, will the ultimate aim of pathology be reached. Disease is the experiment of nature; we see only the results, while we are ignorant of the conditions under which the experiment has been performed. Step by step, pathology must unveil these conditions. It progresses from observation to correlation, from correlation to deduction, in order that rational experimentation may accomplish the final synthesis.

An introductory chapter to a textbook of pathology should not refer to facts which will be presented in detail in the various chapters of the text. This principle has been adhered to not for lack of illustrative material but rather despite an abundance of such material.

Disease manifests itself in alteration of form and function. Anatomic pathology deals with alteration of form, structural as well as material, while alteration of function is the domain of clinical investigation. An integrated knowledge of altered form and function is the ultimate aim of pathology and is the cornerstone of modern medicine. This integration requires not only a knowledge of facts but also a certain attitude of mind which must guide the future physician in the study of disease. This attitude of mind can be developed only if the student is trained to advance from exact observation to correlation of facts and from correlation to deduction. Alteration of structure, as disclosed by anatomic pathology, is easier to perceive than alteration of function; the analysis of changes in structure, as they occur in disease, is therefore a simpler preparation for the inquiry into the mechanism of disease. Moreover, as has been indicated previously, many methods used for the recognition of disease in the living are founded upon the knowledge of structural alterations in the dead. All this accounts for the position of anatomic pathology as a pre-clinical subject and for the requirement that a textbook of pathology shall be devoted primarily to exact description and interpretation of structural anomalies observed in disease. No textbook of pathology with its spatial limita-

tions can fully achieve this object. It can attempt to present in concise form the results of investigation, it can never give a full account of the long road which has led from the original observation of lesions to the understanding of their causation; but by well-chosen references to literature, it can stimulate the student to a historical review of the problems of pathology. Thus the student can spiritually repeat the investigative efforts which have advanced our

knowledge.* In this way he will develop the attitude of mind which will later enable him to make his own contribution to the ultimate object of medicine: to recognize the intrinsic reason of disease.

*It is of great advantage to the student of any subject to read the original memoirs on that subject, for science is always most completely assimilated when it is in the nascent state (James Clerk Maxwell).

Chapter 2

CELLS AND THEIR BEHAVIOR

E. V. COWDRY

FLUID ENVIRONMENT

The body is a complex system of regulated fluid streams in which cells live and function. As indicated in Fig. 1 the principal stream enters the alimentary tract and escapes mainly in the urine. The circulating blood plasma is about 5 per cent of the body weight, the more sluggish interstitial fluid (tissue fluid + lymph) 15 per cent, and the innumerable lakelets of intracellular fluid 50 per cent.

All living cells are aquatic but they are not all bathed in blood as protozoa attached to the rocks of the bed of a stream are bathed in water passing by—a much mistaken simile. Only the endothelial cells which limit the blood stream and the blood cells within it are directly in contact with blood. A fundamental feature in the architecture of the body is the protection of all other cells from direct contact with blood.

The vast majority of cells live in tissue fluids which are shielded from the blood stream by a layer of vascular endothelium through which transfer of material is limited. These tissue fluids are not seen to be of large extent on naked-eye examination, but in relation to the size of their cellular inhabitants they are of considerable volume. They are certainly larger pools of fluid in vivo than when viewed in microscopic preparations in which there has been a shrinkage of 10 to 20 per cent. The preparations are therefore deceptive.

Walter B. Cannon¹⁸ has written eloquently about the factors which maintain like states (homeostasis) in the blood stream. In the tissue fluids, unlike states, or conditions, are established to provide the special fluid environments required by many kinds of cells; and these environments are regulated so that the cells are not subjected to injury by the imposition of too great changes in their manner of life. Thus, heterostasis in the tissue fluids is imposed upon the homeostasis in the blood—a concept which is gaining ground rapidly. These different states in tissue fluids owe their origin and maintenance to local differences in:

1. **Permeability of Vascular Endothelium.**—Exchange between blood and tissue fluid depends on permeability. Where there is a high degree of vascular permeability (spleen and liver), exchange is greater than where it is lower (extremities).

2. **Blood Supply.**—Contribution from blood to tissue fluid and drainage from tissue fluid into the blood also depend on availability of the blood stream to the tissue. From avascular

tissues, such as epidermis, cornea, and cartilage, blood is held at a distance so that their tissue fluids are less conditioned by it than are those of tissues having a rich blood supply.

3. **Lymphatics.**—Some components of tissue fluids unable to leave them through vascular endothelium can get out through lymphatic endothelium because it is more permeable. Tissue fluids of alymphatic tissues (brain, bone marrow, etc.) are consequently less effectively drained than are those provided with many lymphatics (intestinal mucous membrane, dermis, etc.). A good account of lymphatic drainage is provided in *Annals of the New York Academy of Sciences*.¹⁹

4. **Cellular Inhabitants.**—Obviously, their influence on the tissue fluid depends on what they take from it, what they give to it, and whether they are surrounded by much or little of it.

5. **Fibrous Components.**—Where elastic and collagenic fibers exist in the tissue fluids, these may be expected to influence the composition of the fluids because they provide surfaces for adsorption (cf., iron and calcium encrustation in blood vessel walls). Alterations in arterial elastin with age cannot fail to influence the composition of the surrounding tissue fluid.²⁰

Many peculiarities of different tissue fluids have been reported and others are to be expected.¹ Only those most easily collected have thus far been analyzed. Cerebrospinal fluid differs very materially from joint fluid. The fluid in the anterior chamber of the eye appears to be unique in that species differences are lacking which in other areas are present and prevent successful transplantation into them of tissue from alien species. One of the potentially most useful advances recently made has been the discovery of polysaccharides in the dermal tissue fluids which give them a gel-like consistency so that mechanical resistance is offered to the spread of entering substances whether infective or otherwise. This resistance is overcome by so-called spreading factors which break down the gel. The best known is the factor, hyaluronidase, acting on the polysaccharide, hyaluronic acid.²

To be more precise, tissue fluids are of two orders. The first and basic order of tissue fluid is simply separated from the blood stream by vascular endothelium. This is represented in light stipple in Figs. 2 and 3.

The second order of tissue fluid is separated from the blood stream by vascular endothelium, plus tissue fluid of the first order, plus another

membrane. In the case of intraocular tissue fluid, one of the second order, this membrane is ectodermal epithelium; while in the case of peritoneal tissue fluid, likewise one of the second order, this membrane is mesothelial.

KINDS OF CELL LIVES

In addition to an appreciation of local tissue fluid environments as controlling factors in cellular behavior, it is important to remember that fundamental differences exist in the kinds of lives which cells live. From this point of

view there are two great classes of cells, each divisible into two subclasses, making four kinds in all.³

1. Intermittotics.—These cells exist as individuals from the mitosis which gives them birth to the next following mitosis when each divides forming two other individual cells. Their intermitotic lives do not end in death but in cessation of individuality. They do not become senile, but throughout their lives are young.

Some intermittotics are through long years the reservoirs in the body of new cellular life.

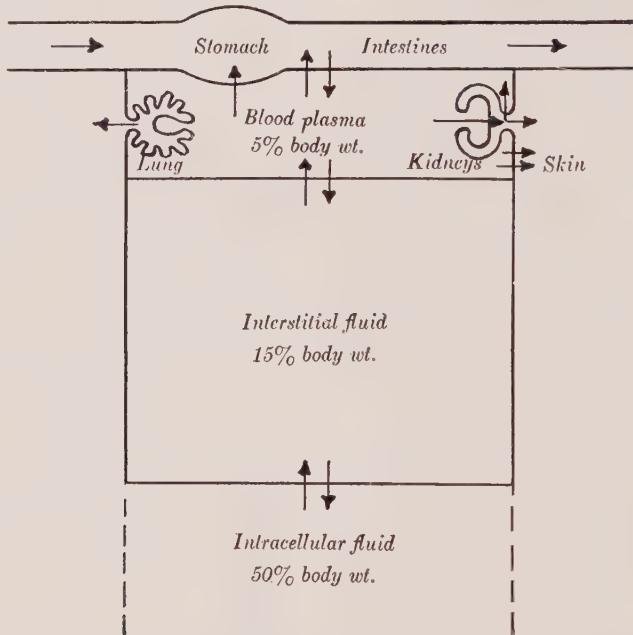


Fig. 1.—Proportions of body fluids. The interstitial fluid includes both tissue fluid and lymph. (From Cowdry, Textbook of Histology, Lea & Febiger, 1944, after Gamble, 1937.)

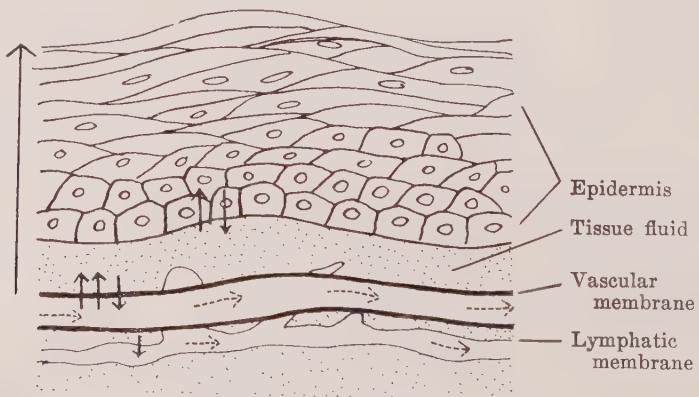


Fig. 2.—Histologic relations of dermal tissue fluid represented in light stipple. The broken arrows show direction of flow of blood and lymph, and the small solid arrows the movements of tissue fluid. The large vertical solid arrow suggests the direction of a deprivation gradient in the tissue fluid. (From Cowdry, Problems of Ageing, Baltimore, 1942, Williams & Wilkins Co.)

These are the *vegetative intermitotics*. The primitive blood cells—whatever hematologists may ultimately decide that they look like or may call them—end their individual lives when they divide, each producing two others. Among these daughter cells some remain in the same place and repeat in their persons the same vegetative kinds of lives.

Other daughter cells are perhaps edged a little away from their birthplace, and in the tissue fluid are subjected to slightly different conditions so that their lives are altered. These, in turn, are the *differentiating intermitotics*. When they divide, their daughter cells carry on from about the stage of differentiation which their parents attained, and they pass on to their own descendants the still higher stage of differentiation which they themselves achieve.

do divide—kidney cells for example, when many other kidney cells have died or have been excised—so cells possessing this property are called *reverting postmitotics*. Smooth muscle cells and several others will be found to belong to this same category.

Nerve cells (in children after about 2 years of age), neutrophilic leukocytes, corneal cells of the epidermis, and a host of others cannot revert to a state capable of mitosis and are, therefore, known as *fixed postmitotics*. Inevitably, these age and die but at different rates. Individual nerve cells, for instance, live several thousand times as long as leukocytes. Their lives are terminal. We look to all others, but not to fixed postmitotics, as possible sources of cancer.

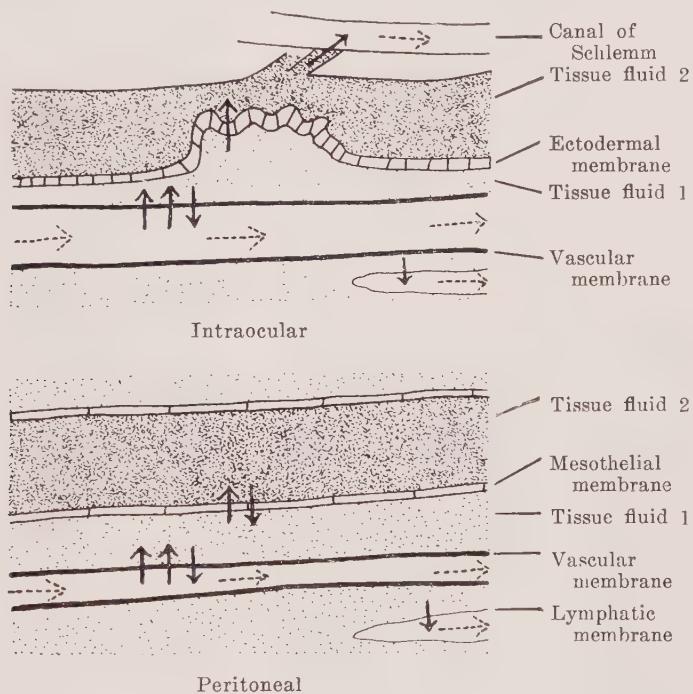


Fig. 3.—Intraocular and peritoneal tissue fluids of second order in dense stipple. (From Cowdry, Problems of Ageing, Baltimore, 1942, Williams & Wilkins Co.)

It is an interesting exercise to survey the cells of the body in search of still other vegetative and differentiating intermitotics, many of which will be found. Among the former are basal cells of the epidermis and spermatogonia of the testicle, and among the latter, spinous epidermal cells and spermatocytes.

2. Postmitotics.—By contrast these cells do age and die. Their lives are ordinarily postmitotic, not intermitotic. They are highly specialized cells, completely fitted by their differentiating intermitotic ancestors to serve in many capacities—secretion, conduction, and so on.

However, some of them can, if the demand is urgent, revert to a condition in which they

TYPES OF CELLS

Nobody knows how many different types of cells exist in the body, but there are two large groups—the “surface cells” and the “fill-in cells.”

The surface cells make up epithelium, endothelium, and mesothelium. *Epithelium* enjoys the position of seniority as to date of introduction, since this term can be traced to Ruysch in 1703. As now used, it covers: (1) cells closely packed together side by side in single or multiple layers which invest external or internal surfaces, and (2) other cells, which, in the course of development, have moved away from such surfaces but remain rather close together. The tissue fluid

between them is generally small in amount. It is the nature of epithelial cells to be concerned with protection, absorption, secretion, excretion, as well as with conduction, for nerve cells are of epithelial origin (ectoderm).

The term, *endothelium*, was proposed by His in 1865 to describe the much flatter layer of cells which lines blood vessels and lymphatics.

Mesothelium is the youngest term of the three, having been suggested by Minot in 1890 to describe the equally thin and delicate layer of cells which limits the principal body cavities—pericardial, pleural, and peritoneal. Some believe that endothelial and mesothelial cells can become detached from the respective surfaces and move about as individuals, but epithelial cells generally remain in sheets, cords, tubes, or dense masses and exhibit polarity.

The "fill-in cells" are highly diversified. They include muscle cells which are ordinarily intimately bound together with but little intervening tissue fluid. In this respect, of being closely packed, muscle cells are like epithelial cells though only those of the iris muscles are of epithelial (ectodermal) origin. In bone and cartilage the cells are more separated. Between them in the tissue fluid are fibers, minerals, and other substances giving firmness. Other cells of connective tissue lineage are free to move about. The tissue fluids they inhabit are not thickly populated; oxygen consumption per unit volume is, therefore, lower than that of epithelial tissues. Because these cells of loose connective tissue do not stay put, and have an extraordinary capacity for changing their appearance in response to alterations in their fluid environments, their classification is extremely difficult. Some store fat, and these, like monocytes, look very different when engorged. Invading white blood cells complicate matters for they also change their appearance.

This is not the place to describe cellular peculiarities. Only to be stressed is the structural and functional contrast between sessile "surface cells," closely applied, exhibiting polarity together with minimum intervening tissue fluid, and the "fill-in cells," mostly of middle layer (mesodermal) origin, not similarly moored but usually located in generous quantities of fluid. It is these tissue fluids that develop the most marked local differences in composition and consistency, being often pervaded with fibrous structures.

STRUCTURE OF CELLS

All cells, of whatever type, are limited by cell walls. The cytoplasm within is protected in some measure from the tissue fluid without, just as this fluid is protected by vascular endothelium from unrestrained mixture with blood. These walls can be said to constitute the second level of membranous separation. Inside the cells the fluid is poor in sodium and chloride and rich in potassium and magnesium—the reverse of what obtains extracellularly. A multitude of other differences between cytoplasm and tissue fluid could be listed.

The essential part of all cell walls is the *plasma membrane*. This conditions permeability,

and its integrity is essential to cell life. It is said to consist of a continuous layer of lipoid molecules (phosphatids, sterols, fats) not more than 2 to 4 molecules thick, on which proteins are adsorbed. The lipoid molecules are arranged radially and give permeability, while the protein molecules are disposed tangentially and give mechanical strength. At least, this is the general idea, based largely on polarization optical studies. Certainly, the plasma membrane is very thin, so thin as to be beyond the limits of microscopic visibility with ordinary light. However, in practice, its position is clearly outlined as the surface of separation between two optically different fluids, one inside and the other outside of the cell.

Sometimes the plasma membrane is strengthened externally by other much more robust investments. One calls to mind ova, parts of nerve cells, muscle cells, and plant cells. On the inside of the membrane, or within its substance, it is generally assumed that the peripheral cytoplasm has gel-like consistency. This is the *plasma-gel layer* discussed in such an interesting way by Lewis.⁴ Since gelated colloids *in vitro* automatically exert contractile tension, he believes that the plasma-gel layer does likewise, that uniform tension is responsible for spherical shape of cells, and unequal tension for ameboid movement and cell division. The analysis by Lewis⁵ of the shifting of chromosomes in mitosis, so clearly demonstrated in moving pictures, and of many other phenomena related to changes in viscosity, will repay careful reading.

Probably not all plasma membranes are of identical composition or permeability. Presumably both these properties differ somewhat as between different kinds of cells and different functional states in the same cell. Neither must all materials entering or leaving cells necessarily pass through the plasma membranes, though most of them do. This fact may explain some of the perplexities of biochemists.

Consider first those materials leaving; for their manner of exit was first seen by Covelle in living acinous cells of the pancreas before the passage of entering ones was detected. He observed some granules of secretion antecedent moving out toward the lumen of the duct within extensions of the plasma membrane, which extensions, with the contained granules, later became pinched off, leaving behind an intact plasma membrane. In such cases, investments of plasma membrane left the cells with the secretory product and afterward broke down. We are here concerned not with the frequency or regularity of this mode of exit but with the fact that it does happen. Another example of the same phenomenon has been fully described by de Robertis⁷ in the thyroid gland.

Entry of materials has been beautifully illustrated in moving pictures by W. H. Lewis under the designation of *pinocytosis*, or drinking by cells.⁸ In this process, extracellular fluid extends into invaginations, or folds, or the plasma membrane which similarly become pinched off from the surface and incorporated into the cytoplasm (Fig. 4). The plasma membrane enters with the incoming fluid and subsequently disappears as such.



Fig. 4.—Pinocytosis by living malignant cell of Walker rat sarcoma 315. Note peripheral ruffle pseudopodia and globules of various sizes moving in a central direction. ($\times 1,100$) (From Lewis, Am. J. Cancer 29: 666, 1937.)

Turning now to the structure of the cytoplasm, its physical consistency and hydrogen ion concentration have been investigated by Chambers and his associates by methods of microdissection and microinjection of indicators. Clues as to physical consistency of cytoplasm can be secured from observing the movements, or lack of movements, of granules and by noting the displacement of contents when cells are subjected to measured quantities of centrifugal force.

Many cytoplasmic components are microscopically visible *in vivo*: pigment, lipoid, inclusion bodies in certain virus diseases, secretion antecedents, specific granules of leukocytes, mitochondria, and so on. Others can only be readily seen in fixed preparations: Golgi apparatus, neurofibrils, Nissl substance; but these are not entirely figments of the imagination for they are distinctively located, present only in certain cells to which the techniques are applied, and must therefore have some material existence in fact.

In recent years, revolutionary progress has been made in our knowledge of the ultimate structure of cytoplasm. Space permits reference

only to the high lights, though all these newly established facts will be the basis of pathology as it expands.

Fluorescence results from the ability of some substances to convert invisible ultraviolet light of short wave lengths into visible light of long wave lengths. For example, when exposed to ultraviolet light, vitamin A emits a quickly fading green fluorescence, certain polycyclic cancer-producing hydrocarbons emit a ghostly bluish fluorescence, while porphyrins show red to orange fluorescence. This is helpful because there are no histochemical tests for these substances, but their accurate identification depends on the quality of the emitted light as revealed by spectra of the fluorescence. This kind of fluorescence is said to be "primary." It differs from "secondary" fluorescence exhibited by certain materials in ultraviolet light after sensitization by fluorchromes. The dye, auramine, is the fluochrome used to bring out the golden-yellow secondary fluorescence of tubercle bacilli. Fluorescence microscopy is destined to be of great service to pathologists. It brings out a change, not otherwise detectable, in mast cells accumulating in precancerous lesions caused by methylcholanthrene,⁹ and it is advocated as a means of demonstrating cell injury.¹⁰

Many mineral components of cells cannot be detected by ordinary methods. When, however, the organic substances are burned out, the

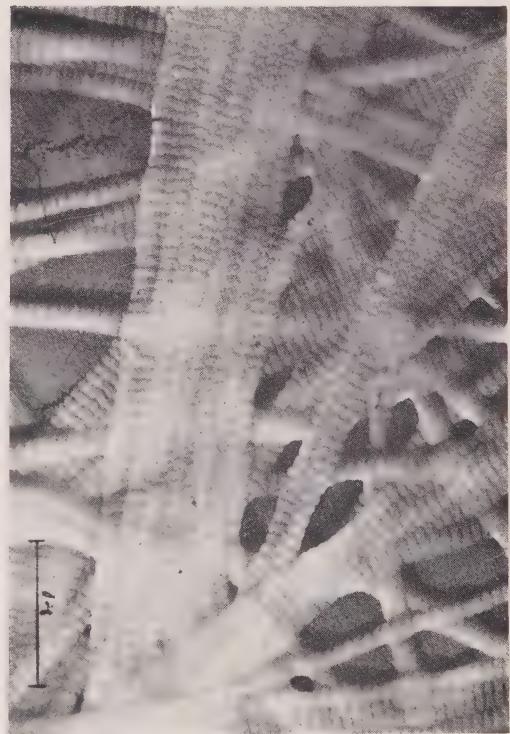


Fig. 5.—Human skin collagen shadowed with chromium, viewed by electron microscope ($\times 19,500$). (Photograph by Dr. J. Gross, Department of Biology, Massachusetts Institute of Technology.)

minerals, which are not volatile at the high temperature used, remain in the position which they originally occupied and can be seen by the light which they reflect when the sections are examined in the dark field. The richness of nuclear substance in minerals, the great difference in mineral composition of the dark and light bands in muscle cells, and many significant features in the make-up of arterial walls¹¹ have been discovered by this technique.

striations is definite and characteristic for some kinds of fibers.¹² (See Fig. 5.) This gives us hope that pathologists eventually will be able by electron microscopy to determine the quality of collagenic fibers, just as engineers can that of steel.

Isolation of cell components and their direct analysis has proved of great assistance, particularly in the hands of R. R. Bensley and his associates. (See summarizing paper by

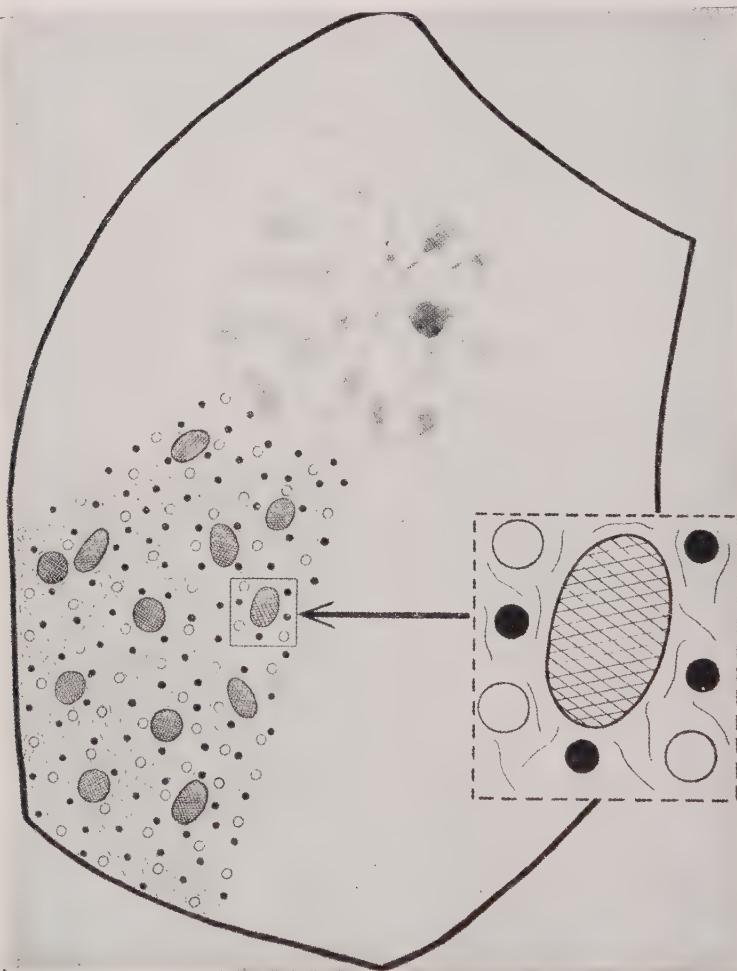


Fig. 6.—Schematic view of liver cell showing nucleus, cytoplasm, and cell membrane. Mitochondria, large cross-hatched bodies; submicroscopic lipoprotein complex, small solid spheres; particulate glycogen, hollow spheres; asymmetric micelles probably responsible for sol-gel changes, long narrow threads. (From Lazarow, Biol. Symposia 10: 1943.)

Electron microscopy gives us far greater magnifications than ever before. The limit of practical usefulness is 70,000 to 100,000 times, but smaller magnifications than this are generally used. Examination by this means has brought to light details in the structure of virus particles not before suspected. Perhaps the most significant discovery for pathologists is that collagenic fibers are made up of fibrils which are cross striated. The spacing of the

Lazarow.¹³) The isolation is effected by centrifugation and appropriate washing after the cells are broken up. Three cytoplasmic fractions thus collected differ in their color. The mitochondria en masse are yellow, rich in lipid, vitamin A, and the succino-oxidase system of enzymes. Particulate glycogen is white. Submicroscopic particles of lipoprotein are cherry red. Other submicroscopic components include asymmetrical wormlike molecules of plasmosin (desoxyribose

nucleic acid) said to be responsible for gel-sol changes and long, thin rodlike nucleic acids, about 300 times as long as they are thick. In the continuous aqueous phase between these components are the soluble proteins, metabolites and electrolytes (Fig. 6).

Islets of protoplasm are isolated from the cytoplasm as nucleoplasm within nuclei. Nuclear membranes constitute, indeed, the third and innermost great protective and at the same time integrating investment in organization of the body, the other two being the endothelial membranes and plasma membranes already alluded to.

Little is known about the molecular composition of nuclear membranes, but they are certainly strongly built; because, when the plasma membranes are ruptured and the cytoplasm fractionated by repeated washing and centrifugation, nuclei freed of cytoplasm can be collected and examined. After this rather strenuous treatment, not only are their membranes seemingly intact but surprisingly slight changes are evident in their size, shape, and internal structure. Perhaps the most outstanding separation has been Ziegler's¹⁴ collection of pure nuclei from epidermis—an epithelial tissue in which the cells are particularly firmly bound together. Quantitative studies on permeability of membranes of isolated nuclei are long overdue.

There can be no doubt that the tiny gel-like masses of nucleoplasm, protected by these membranes, are citadels of conservatism in the body anatomic. Here reside the genes which have shaped cellular structure and behavior for so long, yet which may mutate, perhaps with disastrous results, fixing a new and malignant behavior on the cells and their descendants, or with the appearance of traits having definite survival value, or of still other characters which are passed by unnoticed.

One point, not to be lost sight of, is that the chromosome contents in genes of all somatic cells of a single developing individual are normally the same. Local differential influences acting on the cells in their tissue fluid environments are responsible for specialization in different directions despite this similarity in hereditary nuclear endowments conserved and protected by these innermost membranes. If these intimate fluid surroundings were, in fact, of substantially uniform composition throughout the body, as was tacitly supposed by physiologists until recently, they would have exercised an influence dictating cellular uniformity.

Any concept of cell life which ignores these tissue fluid environments and the roles of the three membranes, endothelial, plasma, and nuclear, is narrow indeed. The Greek, Thales, told us truly that "Water is the mother of all things." Basic integration of our billions of cells is by nicely regulated water-borne traffic. Even superposed, rapid nervous integration is effected by liberation of chemical substances in tissue fluid at nerve endings.

FUNCTION OF CELLS

These little aquatic units naturally serve many diverse functions according to their abilities which it would be wearisome here to try to catalogue. Several features of their service are familiar to pathologists. The first is that dead cells also serve. Life of the community of cells

would soon fade away were it not for the protective shield of dead epidermal cells and for transport of oxygen and carbon dioxide by dead red blood cells.

A second is the mode of assignment of duties. Except in the placement of nerve cells for rapid communications, there is nothing remotely resembling a "construction line" in the body. Each cell in its own person is so organized that it can carry through to completion the function which it serves, whether this is manufacture of some needed product, disposal by phagocytosis of particulate material, storage or release from storage of substances useful to the whole cellular community, physical labor by contraction, or something else. Cells are not so placed that by a "sit down strike" they can prevent other cells from completing the job. Volume of labor is realized by multiplicity of units.

A third feature is the provision of a surplus of worker cells and the spread of labor so that unemployment is unknown, though rest periods are arranged. Full advantage is taken of the added force achieved by making activity rhythmic. Thus, Cooper and Schiff¹⁵ have discovered a rhythm in mitosis in the epidermis with peak of maximum frequency of division by night and minimum by day. It is an instructive experience to review bodily activities and classify the rhythms on which life depends, the perversion of which may lead to serious consequences.

The call of cells to duty is little understood. In most instances the messages are chemical substances. These may be precisely directed by liberation at nerve endings or they may be broadcasted, that is, they may be discharged into the blood stream and reach all vascularized tissues whether they are or are not capable of responding. This is less economical of material.

Like radio waves, the broadcasted substances must be penetrating. In the phraseology of the biochemist, they must all be of small molecular size and highly diffusible, for otherwise they would be held back by the endothelial membrane, go around in circles, and fail delivery to the cells for which they are intended.

Also, as with the radio, reception depends on properly tuned receivers. Differential cellular responsiveness is a fundamental attribute without which the broadcasted messages would create hopeless confusion. There is evidence that the responsiveness is not always of the same degree but may be in some measure subject to rhythmic changes. A logical introduction to pathology would be a complete list of established hormones with the kinds of cells which respond to each because so many pathological conditions can be traced to detectable excess or inadequacy of broadcasted hormone and to increases or decreases in specific responsiveness which are so much more difficult to identify.

This differential cellular responsiveness is also the springboard of *compensatory hyperplasia*. Red cells, blood eosinophiles and neutrophiles are all of marrow origin. When more red blood cells are demanded to compensate for loss, their progenitors respond to a call which is not felt by the ancestors of the eosinophiles or by those of the neutrophiles. The two latter respond each to specific calls. Yet all three must be exposed to the new conditions which evoke the responses and which are probably broadcasted throughout the blood stream.

Another category of calls to duty involves messages which are, at least initially, physical in nature. The efficiency of sense cells is conditioned by the fact that they respond to influences to which others turn a deaf ear; their threshold of reactivity is lower.

Normality of cells, of the tissue fluids in which they live and of the fibrous components in these fluids, is defined as the usual state or the condition in 50 per cent or more of instances in similar circumstances. This qualification "in similar circumstances" is obviously essential, because what is normal at one age, may not be normal at another age. Not only the age but also the sex, the race, the geographic environment, and other factors must also be similar.

When the function of a cell is normal, its structure is also normal, and vice versa. The two are one and inseparable. Concept of structure extends far beyond the limits of microscopic vision to all organization in space, and of function to all the consequences of this organization whether observable or not.

REPLACEMENT

Marvelous mechanisms exist for the replacement of parts. In a motorcar, performance decreases as the part wears out until conditions get so bad that a complete new part has to be substituted for the old one.

The efficiency of the living components of the body is by contrast maintained for many years. Cells of the postmitotic varieties are either very long-lived and present in excess of needs, so that some can die off without impairing collective function, or are short-lived, in which case others are being continually supplied from permanent vegetative intermitotic reservoirs via numerous lines of differentiating intermitotics.

But the efficiency of the nonliving elastic fibers does run down, at different rates depending upon the differential action of alterations in their local tissue fluid environments and on mechanical factors of strain breaking down their elastic colloidal consistency. Worn-out fibers are not properly disposed of and new fibers cannot adequately take their places. The factors in aging of collagenic fibers, and of kindred reticular fibers, remain a virgin field for research.

So much for the cells and fibers that can be seen microscopically. Replacement is not a gross matter limited to them, but is almost all-pervasive. In the past ten years our view of replacement has been expanded by employing the device of offering to the tissues marked materials and by observing how these are received.

Schoenheimer¹⁶ marked fatty acids by including in them heavy hydrogen (deuterium). In some of his experiments old fat was replaced by new marked fat in six days. He showed that most dietary fat is not oxidized directly but is first stored in the fat cells of the great depots. From this it appears that Nature is a good housewife. She uses up the old fat while storing new fat for use later. The turnover of fat in man may not be as rapid as in Schoenheimer's mice, but we can no longer consider

fatty tissue as static. The speed with which individual fat cells store and discharge fat has been determined by the Clarks.¹⁷

Elements made radioactive by cyclotrons have been widely used. These are apparently accepted and eliminated by the tissues in the same way as are the same elements in non-radioactive condition. Their intake can be measured by the Geiger-Müller counter, and, since the total amount of the element in the tissue is not increased, the outgo is the same as the intake, so that the intake is a measure of the replacement. Opportunities for study are numerous and enticing. The general trend of results indicates that many components of cells and tissue fluids, including the ground substance of cartilage and bone, are replaced at rates nicely adjusted to their needs. A limit cannot be set to the process. Because individual nerve cells endure so long is no reason to suppose that much of their substance is not replaced. Cytoplasmic ribonucleic acid making up the Nissl bodies is in fact rapidly replaced while nuclear desoxyribonucleic acid is replaced very slowly. Orderly replacement is what maintains cellular structure and fluid environment in good condition and relatively stable. Nothing living is, of course, actually stable. Life is the continuing effort to maintain equilibrium against forces tending to upset it.

References

- Cowdry, E. V.: Problems of Ageing, Baltimore, 1942, Williams & Wilkins Co., p. 936 (ageing of tissue fluids).
- Miner, R. W. (Editor): Ann. New York Acad. Sc. 52: 945, 1950 (ground substance of mesenchyme and hyaluronidase).
- Cowdry, E. V.: Problems of Ageing, Baltimore, 1942, Williams & Wilkins Co., p. 936 (ageing of tissue cells).
- Lewis, W. H.: Science 89: 400, 1939 (viscosity and cell activity).
- Lewis, W. H.: Monograph of Society of Plant Physiologists, The Iowa State College Press, 1942, p. 163 (relation of viscosity changes of protoplasm to ameboid locomotion and cell division).
- Covell, W. P.: Anat. Rec. 40: 213, 1938 (pancreatic secretion).
- de Robertis, E.: Anat. Rec. 84: 125, 1942 (thyroid secretion).
- Lewis, W. H.: Am. J. Cancer 29: 666, 1937 (pinocytosis by malignant cells).
- Cramer, W., and Simpson, W. L.: Cancer Research 4: 601, 1944 (mast cells in experimental skin carcinogenesis).
- Herick, F.: Protoplasma 32: 527, 1939 (fluorescence microscopy).
- Scott G. H.: Biol. Symposia 10: 277 1943 (mineral distribution in cytoplasm).
- Schmitt, F. O., Hall, C. E., and Jakus, M. A.: Biol. Symposia 10: 261, 1943, and J. Cell. and Comp. Physiol. 20: 11, 1942 (ultra-structure of protoplasmic fibrils).
- Lazarow, A.: Biol. Symposia 10: 9, 1943 (chemical structure of cytoplasm).
- Ziegler, D. M.: Anat. Rec. 91: 169, 1945 (collection of nuclei of epidermal cells).
- Cooper, Z. K., and Schiff, Alice: Proc. Soc. Exper. Biol. & Med. 39: 323, 1938 (mitotic rhythm in human epidermis).
- Schoenheimer, R.: Harvey Lectures 32: 122, 1937.
- Clark, E. R., and Clark, E. L.: Am. J. Anat. 67: 255, 1940 (new formation of fat).
- Cannon, W. B.: The Wisdom of the Body, New York, 1932, W. W. Norton & Co., Inc.
- Miner, R. W. (Editor): Ann. New York Acad. Sc. 46: 679, 1946 (lymph).
- Lansing, I. A., Roberts, E., Ramasarma, G. B., Rosenthal, T. B., and Alex, M.: Proc. Soc. Exper. Biol. & Med. 76: 714, 1951.

Chapter 3

INFLAMMATION

MORTON MCCUTCHEON

Whenever tissue is injured, whether burned, torn, cut, or infected by microorganisms, there follows a series of tissue reactions at the site of injury. These reactions tend to destroy, or limit the spread of, the injurious agent, and to repair or replace the damaged tissues. These local reactions to injury constitute inflammation.

INJURY

Cells and tissues are continually receiving different kinds of stimuli, some of which come from outside the body, such as mechanical and thermal stimuli, while others are internal, such as stimuli that act on muscles and glands. These stimuli excite appropriate reactions, such as narrowing or widening of blood vessels, contraction of muscles, secretion of glands. If, however, stimuli are excessive, either in intensity or duration, cells are injured. Thus, too strong thermal stimulation causes burns; mechanical stimulation, if excessive, causes bruises, cuts, or tears.

Injury may be defined either as excessive stimulation, or it may be regarded rather as the effect on cells and tissues of excessive stimulation. Injury may be manifested by such gross changes as loss or death of tissue in mass, or, if slight, merely by subtle changes in individual cells. These cellular changes include gelation of the protoplasm, increase in permeability of the cell surface,⁶⁰ often with escape of substances from the cell which alter functions of surrounding cells (these substances will be discussed later). For a discussion of the chemical changes occurring in injured cells, see the treatise of Heilbrunn.⁴⁰

Injurious agents may be living, such as microorganisms, or nonliving, such as mechanical agents (e.g., missiles), thermal (heat, cold), radiant (ultraviolet and x-rays), electrical, chemical (e.g., cauter-

izing chemicals). To the injury caused by any of these agents the surrounding tissues react, and this reaction constitutes inflammation. Injury is followed by inflammation; inflammation is preceded by injury.

Primitive Reactions to Injury

In man, as in vertebrates generally, the picture of inflammation is dominated by reactions of blood vessels. Vascular changes are responsible for redness, heat, and swelling,* the familiar signs of inflammation. More primitive responses to injury appeared in the course of evolution long before animals developed a vascular system, and these primitive reactions have persisted down to man himself. For our understanding of these reactions in protozoa and invertebrates, we owe much to Metchnikoff,⁶⁸ and his book on the *Comparative Pathology of Inflammation*.

Even *protozoa* react when injured. If an ameba is cut in two, the portion containing the nucleus regenerates and, in due time, goes on dividing. Regeneration, then, is a primitive reaction to injury, and in man we shall encounter this reaction in the repair of wounds.

Many *protozoa* are attacked by parasites that live inside the larger organism and at its expense. The host reacts by attempting to digest the parasites and to eject the residue. In man, one of the most important ways of destroying microorganisms is by intracellular digestion.

Among primitive *metazoa*, such as sponges, foreign particles are ingested (phagocytized) by wandering ameboid cells of the mesenchyme. In these primitive forms phagocytosis is primarily a feeding process, and only secondarily is phagocytosis useful in ridding the organism of injurious foreign bodies. In higher animals, including man, phagocytosis is no longer a means of feeding, but has become the most important way of reacting to injury. As in the primitive forms, phagocytosis in man is performed chiefly by cells of the mesenchyme. The mesenchyme is the chief tissue to react to injury.

*The "cardinal signs" of inflammation are redness (rubor), heat (calor), swelling (tumor), and pain (dolor) (Galen), together with altered function (taesa functio) (Celsus).

If, in primitive animals, a foreign body such as a splinter is too large to be ingested by a phagocyte, the ameboid cells surround it and, by fusion, form a syncytium. The same response occurs in man and results in the formation of foreign body giant cells.

In *Daphnia*, a small crustacean, is sometimes found a yeast infection. On the ability of ameboid cells to phagocytize and destroy the yeast depends the recovery or death of the crustacean. Similarly in man, infection not only by yeasts, but especially by bacteria, is combated chiefly by phagocytosis and intracellular digestion.



Fig. 7.

Fig. 7.—Inflammation of skin resulting from x-ray burn is here characterized by lymphocytic infiltration of corium and nuclear degeneration of epidermis with vacuolization. ($\times 150$.)

Fig. 8.—Phagocytosis of human erythrocytes by *Endamoeba gingivalis*, a parasitic ameba found in the mouth of man. Several phagocytized erythrocytes are seen as dark circular objects in vacuoles. The nucleus of the ameba lies in the constricted middle portion. ($\times 2,000$.)

Among insects,¹⁰ phagocytosis is the most important reaction against injury. Humoral antibodies are often present and may help resist infection, though they are less potent than in mammals.⁴¹ Segregation also occurs, whereby masses of bacteria or other undigestible foreign bodies are surrounded by concentric layers of blood cells, forming a nodule. The nodule becomes encapsulated by fibrous tissue, and may remain throughout metamorphosis.

Just as foreign bodies are segregated in insects, so lesions in man are often encapsulated, e.g., in tuberculosis and in silicosis.

The earthworm,⁹ unlike the animals already mentioned, has a closed vascular system. Even

so, the blood vessels do not take part in the inflammatory reaction as do those of vertebrates. In the earthworm, if the body wall is injured, the cells lining the body cavity proliferate and migrate toward the injured tissue. Connective tissue proliferates abundantly, and all involved tissues regenerate. Blood vessels grow into these tissues to some extent, but only during repair.

Autotomy (self-amputation) of badly damaged segments is common in worms, and recalls mutilations in man such as are encountered in leprosy and ankhum.

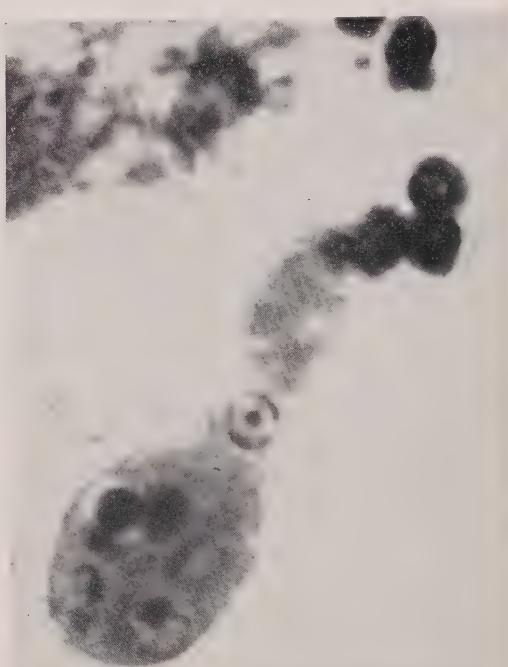


Fig. 8.

Thus, when invertebrates are injured, blood vessels, even if present, rarely react. We find no "cardinal signs" of inflammation. We do find regeneration, phagocytosis, intracellular digestion, humoral antibodies, and segregation, and these are the fundamental reactions to injury in man as well. But in man, and among vertebrates generally, blood vessels not only react to injury but actually dominate the inflammatory process. The great advantage of this vascular reaction is that it hastens and intensifies the inflammatory response, enabling enormous numbers of phagocytic cells to be delivered speedily to the injured tissues, together with antibodies which augment phagocytosis.

INFLAMMATION IN VERTEBRATES: VASCULAR CHANGES

In the vertebrates inflammation is complicated by participation of the blood vessels. This response of the vessels will be described first as it occurs in the mesentery of the frog (Cohnheim experiment, 1867),¹⁸ though the same changes may be observed in the tadpole's tail or fins, or the mesentery of small mammals. In all of these, the tissues are transparent, so that the circulatory bed may be observed with the microscope.

and these permit only one or two columns of cells to pass so slowly that individual cells are distinct.

The reaction of blood vessels to injury begins within a few minutes, due to handling and slight drying of the tissues while the preparation is made. The reaction consists of widening of the vessels, increased capillary blood pressure, and usually accelerated rate of flow.⁴⁹ Capillaries previously empty, and therefore unnoticed, become filled with blood, making the mesentery and intestinal coils red.

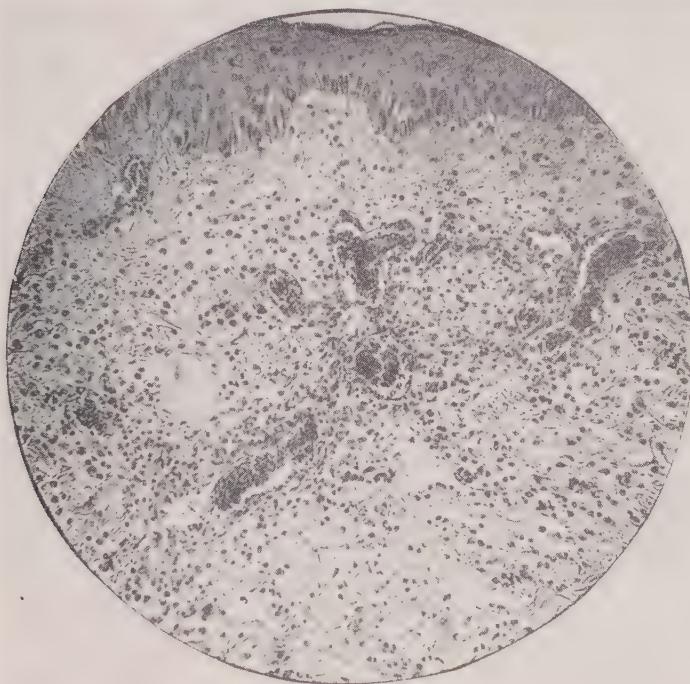


Fig. 9.—Dilatation of blood vessels of human skin during acute inflammation (erysipelas). Blood-filled vessels of the corium appear as dark areas. The tissues are infiltrated with leukocytes. (Courtesy Dr. F. D. Weidman.)

In the Cohnheim experiment, after destroying the central nervous system, the observer opens the frog's belly and gently lifts the mesentery onto a cover slip, so that the mesentery may be viewed with transmitted light as the preparation rests on the stage of a microscope. Through the microscope, blood is seen rushing through the relatively narrow arteries in one direction, while in the opposite direction it flows more slowly through the broader veins; capillaries also are seen,

These changes mean that arterioles have dilated, probably from axone reflexes.

If the mesentery is more severely injured, as by allowing it to dry more, or by irritating it with a small drop of croton oil, or touching it with silver nitrate, further changes appear. Velocity of flow in capillaries and veins progressively decreases, while individual blood cells become plainly visible in veins as well as in capillaries. Finally, in some vessels, there is complete stasis, and such capillaries

and veins are solidly packed with stationary blood cells. These vessels no longer contain plasma; only the cells remain. This fact explains the progressive slowing of the current: as plasma escapes into the tissues, and blood cells become more concentrated, the viscosity of the blood increases enormously, with consequent slowing and finally stasis.

Increase in Permeability of Vessels

The escape of plasma from vessels in an area of inflammation is due to their increased permeability. Normally, capillaries are fairly permeable to water and crystalloids, and slightly so to blood proteins, but following injury, permeability to all these substances is greatly increased. The amount of fluid escaping from an injured capillary may be seven times the normal amount, as measured by Landis⁴⁹ during direct microscopic observation. Colloids, also, pass out of the injured vessels. Colloidal dyes, like trypan blue, are unable to escape from a normal capillary but do so readily after injury, staining the surrounding tissue. A recently devised method⁷³ for measuring permeability to colloids is to attach radioactive bromine (Br^{82}) to trypan blue and to inject this material intravenously. As recorded by a Geiger counter, Br^{82} does not accumulate in normal tissue, but does so in injured areas, indicating that the dye with its attached Br^{82} has escaped from the now permeable blood vessels.

Such increased permeability is probably due to increased size of capillary pores. As estimated from the known size of particles able to pass through, the size of the pores increases from an upper normal of about 38 angstrom units to values of 50 to 200 angstrom units. Such changes in permeability may be temporary and reversible if injury is not too severe.

As the result, plasma proteins escape from the vessels in abnormally large quantities, at first mostly albumin as its molecule is relatively small, later also the globulins, including fibrinogen. Thereby the mechanism for returning fluid from tissue spaces to blood vessels is disrupted, as it will be recalled that filtration of fluid out of capillaries depends on the hydrostatic pressure at the arteriole end being greater than the effective osmotic pressure of the plasma proteins, whereas,

at the venous end, the colloid osmotic pressure exceeds hydrostatic pressure and so draws fluid back into the vessels (Starling's hypothesis). With escape of plasma proteins, the difference between osmotic pressures inside and outside the vessel decreases, until it nowhere exceeds filtration pressure, so that fluid is no longer drawn back into the vessels.

This has several important consequences:

1. **Stasis.**—As already mentioned, plasma leaves injured vessels while blood cells remain, thereby greatly increasing the viscosity of the blood locally. The result is slowed circulation ending in stasis.

2. **Edema.**—Capillary filtrate, no longer returning to vessels, accumulates outside in tissue spaces and body cavities, constituting edema. Edema causes swelling of inflamed tissue (the cardinal sign, "tumor"). Edema is also recognizable in blisters such as are found in second-degree burns, and in accumulations of fluid in inflamed serous cavities (e.g., pleurisy with effusion).

Edema fluid occurring in inflamed tissue is characterized by high specific gravity, high protein content, and ready coagulability (because of fibrinogen). Such edema constitutes an **exudate**, a term applied to the fluid and leukocytes that escape from blood vessels in inflamed tissue. In contrast to exudate, the term **transudate** is applied to fluid that leaks out of vessels in noninflammatory conditions such as cardiac failure. Transudates have relatively low specific gravity, low protein content, and less tendency to coagulate.

As we have seen, edema in inflamed tissue results from increased capillary permeability. In addition, edema is augmented by increased filtering surface, as all capillaries become filled (normally many may be temporarily empty), and also by increased blood pressure in the capillaries, due to dilatation of arterioles from axone reflexes.

3. **Shock.**—So much plasma may leak out of vessels in inflamed tissue that the total blood volume becomes greatly decreased. The patient goes into shock and may die in consequence. Thus, following experimental burns of the foot, plasma equivalent to one-third of the total blood

volume may escape into the tissues of the injured extremity.³⁴

4. Changes in Lymph Flow.—Since the capillary filtrate can no longer be removed by the blood vessels, it tends to be drained away by the lymphatics, and lymph flow is greatly increased. In experimental animals, following burns, the pressure in the lymphatics of the affected leg may reach 120 cm. of lymph, whereas the pressure in the normal leg may not be great enough to be measured.³⁰

The flow of lymph is especially great following burns, because thromboplastin is not released from burned tissue, and therefore there is little tendency for the exudate to coagulate (i.e., for formation

phatic thrombosis than are staphylococcal infections, and this is thought to explain in part the greater tendency of streptococcal infections to spread. To prevent spread and possible generalization of infections it is important that lymph flow be reduced. This is done most effectively by immobilizing the part.

5. Fibrin Formation.—An important result of increased permeability of blood vessels is that inflamed tissue is flooded with fibrinogen, which, on coagulation, helps to limit infection. This it does sometimes by plugging lymphatics, as just described. Fibrin may form also in tissue spaces where it may help to wall off infection. Especially in serous cavities, such as



Fig. 10.—Exudate in blisters of skin. Two large blisters in the epidermis are filled with protein precipitate. (Courtesy Dr. F. D. Weidman.)

of fibrin) and thus to plug the lymphatics.³⁵ In infections, thrombosis of lymphatics is variable. This is a matter of moment, because if lymphatics remain open they tend to carry bacteria from infected tissue to the lymph nodes and perhaps into the general circulation, with consequent septicemia. It is to be emphasized that such spread occurs via the lymphatics, not the blood vessels. The tissues around the lymphatics become inflamed, and appear as red streaks such as are seen on the flexor surface of the forearm following infections of the hand. Streptococcal infections are, according to Menkin,⁶⁷ less likely to be attended by lym-

the peritoneal, fibrin forms on the serosa and sticks intestinal loops together. This is an important factor in limiting the spread of appendicitis following rupture. As long as these fibrinous adhesions are intact, the remainder of the peritoneal cavity is protected, whereas ill-advised or accidental breaking of adhesions by manipulation may allow peritonitis to become general.

CELLULAR REACTIONS IN INFLAMMATION

Adhesion of leukocytes to vessel wall (margination) occurs as the circulation becomes slower in an area of inflamma-

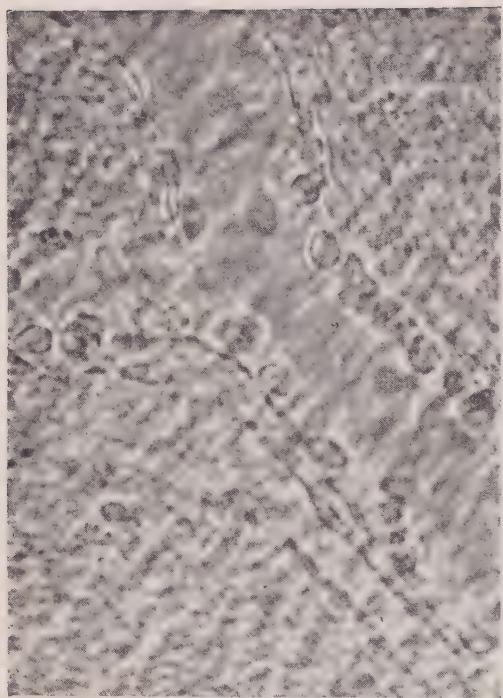


Fig. 11.—Margination of leukocytes in a vein in the rabbit ear chamber. ($\times 760$) (Courtesy Dr. E. R. Clark.)

tion. In the frog's mesentery (Cohnheim experiment), individual leukocytes are distinguishable inside the veins, and are

seen rolling slowly over the endothelial lining. Some of these leukocytes adhere to the vessel wall. Such cells may be pulled loose by the current, but others adhere to the same place. Apparently the endothelium in this part of the vessel has become sticky.¹⁵ More and more leukocytes become adherent until they cover the endothelium and project into the lumen, and thus narrow the blood channel.

Emigration of leukocytes then occurs through the apparently intact vessel wall. First, a pseudopod of a leukocyte is seen outside the vessel, while the rest of the cell remains attached to the endothelium. This pseudopod enlarges, as the leukocyte flows through the vessel wall. Within two to eight minutes, the entire cell lies outside the vein or capillary. In this way scores of leukocytes pass through, and the vessel becomes surrounded by a mantle of emigrated cells. These cells then move away through tissue spaces or, in the case of the mesentery, travel over the surface.

Erythrocytes also go through the wall of the vessel, often in small clusters, spurting through the wall of the dilated vessel. The motion of erythrocytes is passive; that is, they are pushed out by blood under increased pressure through a

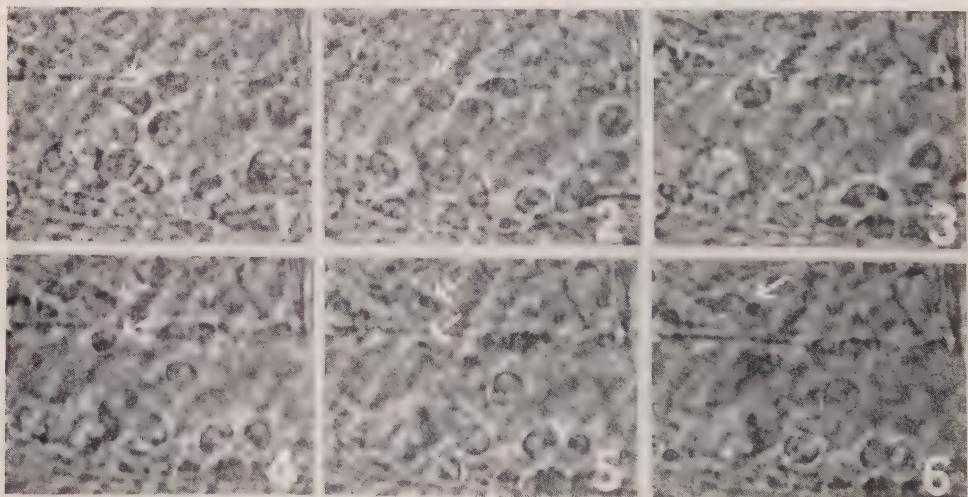


Fig. 12.—Emigration of a leukocyte from a venule in response to mild trauma, as seen in a transparent chamber inserted in the rabbit's ear. Intervals between successive photographs are 36", 2' 24", 1' 36", 12", and 12". Arrows point to emigrating leukocytes. In photographs 1 to 3, cell is mostly in the lumen of the venule, in 4, part of the cell is within the vessel, but a large pseudopod has extended through the vessel wall (upper arrow). In 5, only a small part of the cell (lower arrow) remains within the vessel. In 6, the entire leukocyte lies outside the vessel. ($\times 760$) (Courtesy Dr. E. R. Clark.)

vessel wall that offers less than normal resistance because the endothelium has become softened and defective. Leukocytes, on the contrary, go through the wall by **ameboid motion**, that is, their motion is active, like that of an ameba. While in the blood stream, however, leukocytes show no active movement but float passively and are more or less spherical, whereas in contact with sticky endothelium they spread out, become flattened and begin ameboid motion, and so move actively through the endothelium.

Most writers state that the leukocytes move through the vessel wall because they are attracted by chemical substances outside the vessel, i.e., through chemotaxis. Chemotaxis may aid emigration but it probably is not essential.

A number of other factors have been thought to cause emigration of leukocytes. These factors are chemical and physical differences between the blood inside the vessel and the fluid outside; for example, differences in surface active substances, in hydrogen ion concentration, in electric potential.¹

Chemotaxis⁶²

When grains of starch or other irritant are injected into the tail of the tadpole, leukocytes adhere to the vascular endothelium, emigrate through the vessel wall, and move toward the foreign body.¹³ This directional response or directed locomotion is known as chemotaxis. It means that the leukocytes, instead of wandering at random, move toward the site of injury. The reaction is advantageous, because it enables more leukocytes to reach injured tissue in a shorter time and, in infections, to stop the spread of microorganisms.

Chemotaxis may be defined as a reaction of cells or organisms to substances in their environment, by means of which direction of locomotion is determined. Chemotaxis is positive if the cell moves into higher concentrations of a substance, negative, if it is repelled by the substance and moves into lower concentrations.

Chemotaxis occurs in a great variety of animals and plants. For example, by this reaction, fern sperms are directed toward ova (Pfeffer, 1881-85), and in flowering plants, pollen tubes are similarly directed. Protozoa generally show only negative chemotaxis, being

repelled by injurious substances. Slime molds (*Myxomycetes*) are attracted by edible substances, repelled by some harmful ones. Among metazoa, locomotion may be directed through special chemical receptors. Thus, the male moth is attracted by an excretion from the female, and crabs find their way toward rotten meat. Chemotaxis is accordingly of advantage to the organism in mating, feeding, and avoiding unfavorable conditions.

Chemotaxis in Leukocytes.—The concept of chemotaxis was introduced into pathology by Leber, who in 1888 infected the cornea with *Aspergillus*, and found that leukocytes were attracted by toxic substances given off by the microorganism.

Chemotaxis of leukocytes may readily be demonstrated by the following method: A minute clump of bacteria, such as staphylococci, is placed on a glass slide and allowed to dry. A drop of blood obtained by puncturing the finger is placed on a cover slip. The cover slip is lowered gently on to the slide, so that the blood spreads

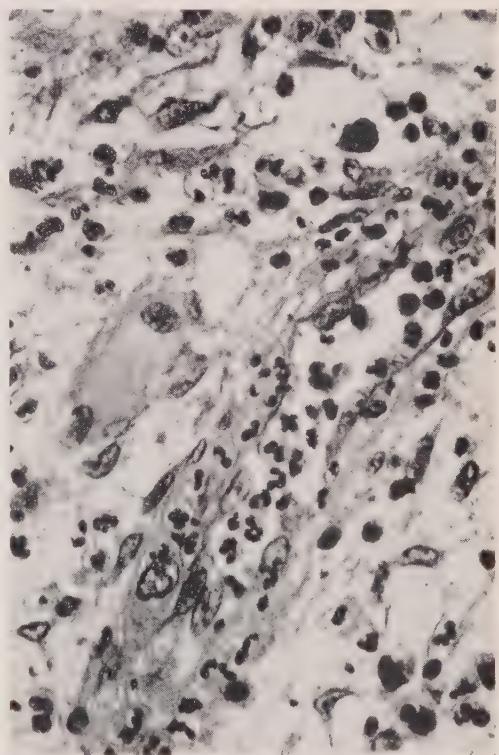


Fig. 13. Emigration of leukocytes in a nasal polyp. The vessel in the center contains a number of granulocytes, others of which are seen in wall of the vessel apparently in process of emigrating. (X640.)

in a thin film between slide and cover slip. The preparation is sealed with petrolatum to avoid evaporation and is examined on the stage of a microscope at blood temperature. Polymorphonuclear leukocytes are seen to begin ameboid motion almost at once. When the paths of those near the clump of bacteria are recorded on paper (with the aid of a camera lucida or similar device), practically all the polymorphonuclear leukocytes (but not the lymphocytes or monocytes) are found to move toward the bacteria until they reach the edge of the clump. The cells then stop and ingest the bacteria.

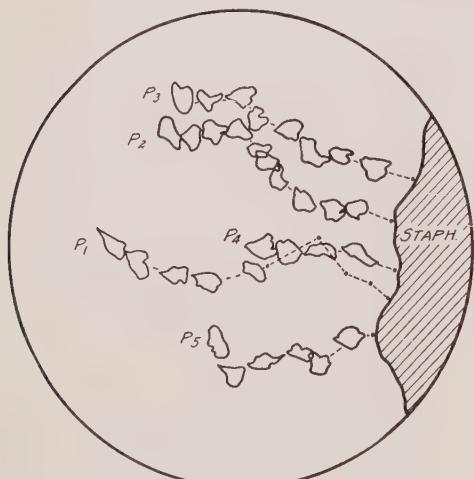


Fig. 14.

Fig. 14.—Positive chemotaxis of leukocytes to staphylococci. Drawings, with aid of camera lucida, of 5 leukocytes in a drop of human blood. The position of each cell is shown at intervals of about two minutes. The cells moved from left to right, toward the staphylococci.

Fig. 15.—Positive chemotaxis of human leukocytes to staphylococci, as observed with the high power of the microscope. The preparation consisted of a drop of blood between slide and cover slip. The initial position of each leukocyte is marked by a circle; subsequent positions at minute intervals are marked by dots. It is seen that all the cells moved toward the bacteria.

The substances that attract leukocytes are chiefly microorganisms and products of injured tissue. Apparently all kinds of bacteria are positively chemotactic, at least for a time, though pus-forming bacteria seem to attract over a greater distance and for a longer time than do typhoid and tubercle bacilli. Little is known about attraction by protozoan parasites, but the plasmodium of avian malaria has been reported to be positively chemotactic. Viruses, so far as is known, do not attract leukocytes. This is inferred from the scarcity of polymorphonuclears in uncomplicated virus lesions.

Chemotaxis to Injured Tissue.—Not only microorganisms but sterile products of injured tissue attract leukocytes. Thus, in sterile blisters resulting from burns, many leukocytes may accumulate.

The chemical mechanism involved is discussed on page 22.

Chemotaxis to Dusts.—To carbon particles, leukocytes are indifferent, being neither attracted nor repelled. Silica also excites no chemotaxis in preparations between slide and cover slip, but when silica is injected into animals, polymorphonuclear and, later, mononuclear cells may be attracted.⁴⁸ This effect is probably due to necrosis caused by silica, releasing chemotactic substances.

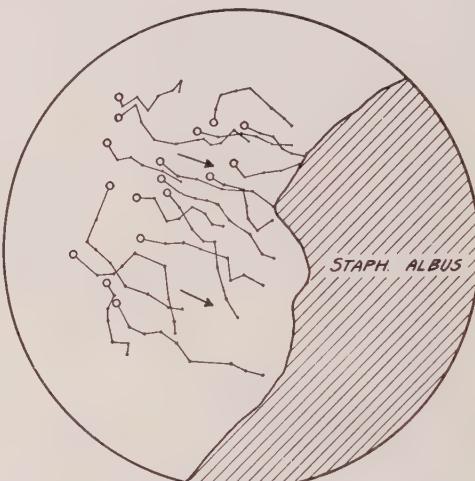


Fig. 15.

Negative Chemotaxis.—There is confusion in the use of this term, some authors meaning by it merely absence of attraction, others, repulsion. Negative chemotaxis should be used only in the latter sense, meaning that cells are repelled by and move away from certain substances. This effect is produced in vitro by particles of certain silicates (not silica) and by silicic acid. The negative reaction to silicate particles is just as intense as is the positive reaction to bacteria, as every leukocyte in the microscopic field moves away from the silicate in an almost straight line. It is not known how or why silicates repel leukocytes.

It is uncertain whether any bacteria repel leukocytes, that is, induce negative chemotaxis. Leukocytes, it is true, may be almost absent from exudate called out by highly virulent bacteria, such as anthrax or Welch's bacilli, or

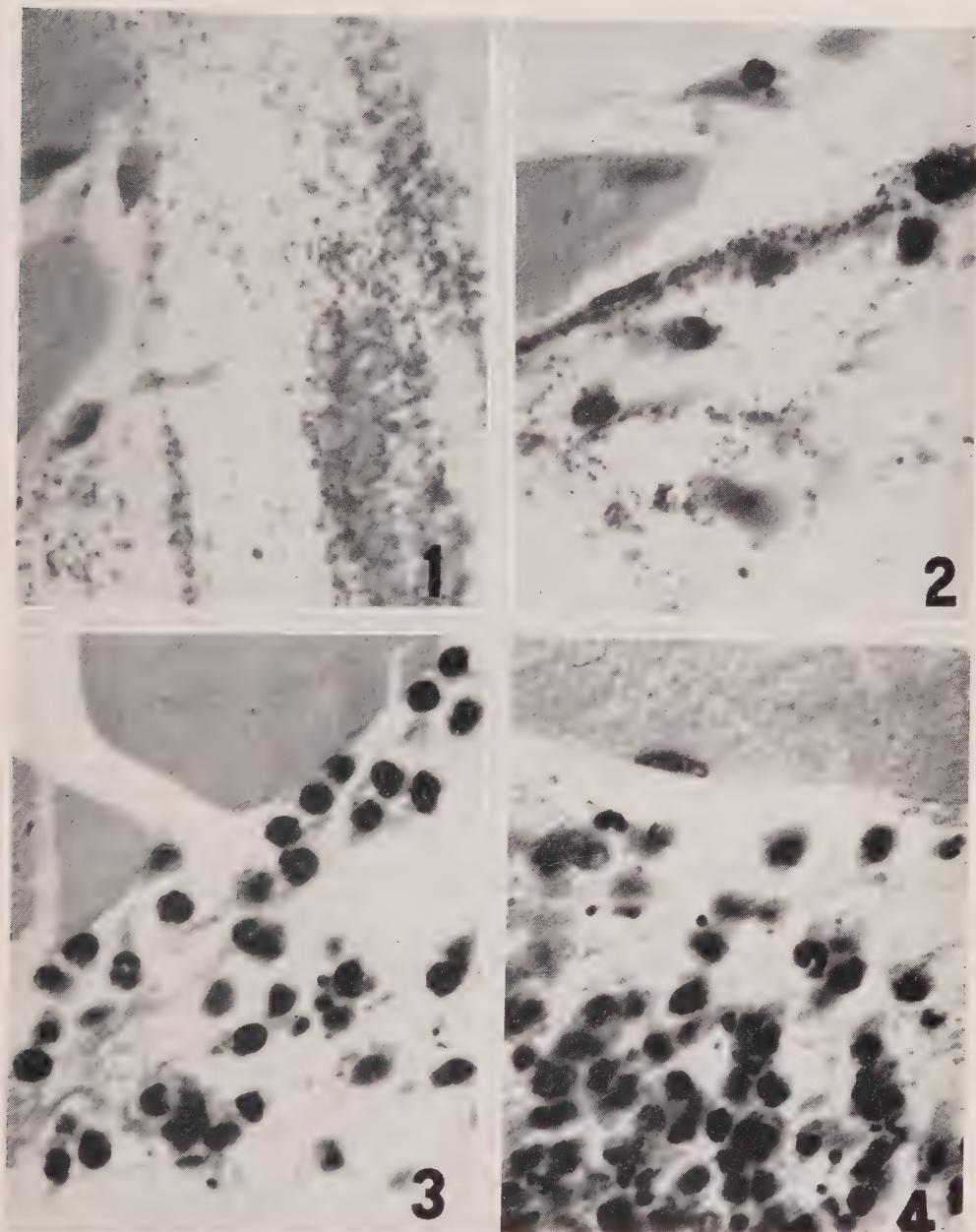


Fig. 16.—Accumulation of leukocytes in leg muscle of mice following injection of dead staphylococci, to illustrate effects of positive chemotaxis. Time intervals after injection: 1 = $\frac{1}{2}$ hour; 2 = 1 hour; 3 = 8 hours; 4 = 24 hours. The successive photographs show increasing numbers of leukocytes, decreasing numbers of bacteria. ($\times 1,050$.)

certain strains of staphylococci or pneumococci, when these are injected into susceptible animals. Such animals promptly die. Under these conditions, leukocytes may fail to appear in the exudate, not because of negative chemotaxis but because they are paralyzed or killed by bacterial toxins.

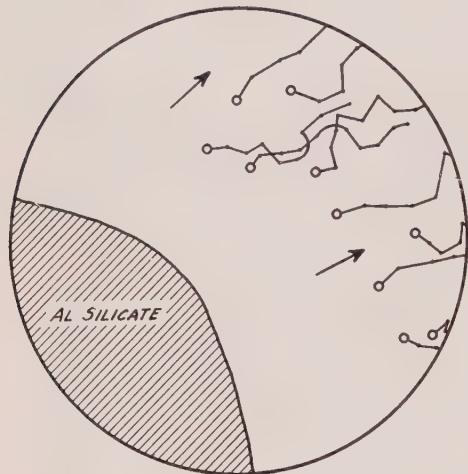


Fig. 17.—Negative chemotaxis of leukocytes to aluminum silicate (Lloyd's reagent). Exudative rabbit leukocytes in plasma. It is seen that all the cells moved away from the silicate. Compare with Fig. 15.

Effect of Immunity on Chemotaxis.—If, however, animals have been immunized against virulent bacteria, or if immune serum is injected along with the bacteria, then even to bacteria of high virulence the leukocytes respond well. This means that bacterial toxins have been neutralized. In such cases leukocytes are able to move normally toward even virulent bacteria, reacting to them with positive chemotaxis.

Effect of Illness on Leukocytes.—When a drop of blood from an acutely ill person is observed with the microscope, leukocytes are seen to move more slowly than normally. Also, they move less directly toward bacteria; that is, chemotaxis is decreased. Supposing leukocytes in tissues to be similarly affected, they would be delayed in reaching bacteria and in preventing their dissemination. These functional changes may be correlated with degenerative granules and vacuoles seen in stained leukocytes. Such degenerated leukocytes are found in patients with severe acute infections, such as lobar pneumonia, and if these damaged cells continue to be found in large numbers, they indicate an overwhelming infection that is likely to kill.

The mechanism of chemotaxis is still far from clearly understood. Earlier writers regarded the leukocyte as a drop of liquid pulled in one direction or another by surface forces. This is almost certainly incorrect. Such an explanation rests on false analogy with the be-

havior of a drop of mercury. A drop of mercury in nitric acid moves toward a crystal of potassium dichromate, and in a solution of potassium dichromate it moves away from a drop of nitric acid, thus imitating a cell displaying positive or negative chemotaxis. The mercury is of course moved by surface forces.

An ameboid cell is something very different. It consists of protoplasm that is continually and reversibly being transformed from the sol state to the gel state. Like certain other gels, protoplasmic gel has the property of contracting, and by contracting it pushes forward liquid protoplasm, thus bringing about ameboid motion. For a detailed explanation of the mechanics of ameboid motion, the reader is referred to the papers of Mast⁶³ and Lewis.⁵⁵

Chemotaxis is a directional reaction superimposed on ameboid motion. This reaction occurs when concentrations of a chemotactic substance are sufficiently different at opposite poles of the leukocyte. The reaction consists in a sol to gel transformation in one end of the cell and a gel to sol transformation in the other. Contraction of gel on sol then causes the leukocyte to move toward the bacteria.

Summary of Chemotaxis.—It should be clearly understood that it is the direction of locomotion that is determined by chemotaxis, not the rate of locomotion. Should no bacteria or other particles be near by, the leukocyte moves just as fast, but keeps changing direction. The advantage of chemotaxis is that leukocytes can be attracted from a distance and be impelled to move in nearly straight lines toward bacteria. Consequently many more cells reach the bacteria and do so much more quickly than they would without chemotaxis. The distance from which leukocytes may be attracted in the body is unknown, but in slide-cover-slip preparations it is about 1 mm. In such preparations, the rate with which leukocytes approach bacteria is 20 microns per minute or less. In mammals it is chiefly the polymorphonuclears that display chemotaxis.

As the result of ameboid motion and chemotaxis, leukocytes in great numbers form a wall about bacteria and so may prevent their spread. They are then in position to phagocytize the bacteria.

Phagocytosis^{75, 6}

Phagocytosis is one of the most important reactions in inflammation, and may be regarded as the culmination of the various reactions already described. Phagocytosis means the process of ingestion by a cell. The term is usually confined to ingestion of particulate matter, that is, microscopically visible objects such as tissue cells (usually dead), bacteria, protozoan parasites, other micro-organisms, and various dusts, pigments, and foreign bodies generally.

Which Cells Are Phagocytic?—As already stated, phagocytosis appears in the simplest forms of animal life as a feeding reaction, whereas, in metazoa, phagocytosis as a defense reaction becomes gradually distinct from feeding and is performed by cells of the mesenchyme.

soids of liver, spleen, lymph nodes, etc., and phagocytize bacteria and other particles brought by the circulation. In the central nervous system, they are represented by the microglia. While the kinds of cells mentioned are the most important phagocytes, all kinds of cells probably are capable of phagocytosis under some conditions.

Methods for Studying Phagocytosis:
The Film Method.—Phagocytosis may readily be observed with the microscope as follows: Leukocytes are obtained by injecting 200 to 300 c.c. of physiological salt solution into the peritoneal cavity of a rabbit. Three to four hours later, the fluid is withdrawn and centrifuged. In the bottom of the centrifuge tube are found great numbers of polymorphonuclears. These leukocytes are then suspended in plasma or serum, and to this



Fig. 18.—Phagocytosis of erythrocytes by a macrophage, photographed during life. Erythrocytes appear as dark circles with double contours. White refractile inclusions are fat droplets. ($\times 1,100$) (Courtesy Dr. W. H. Lewis.)

In man, the important phagocytic cells are of two kinds, neutrophilic polymorphonuclear leukocytes and large mononuclear phagocytes. These two kinds of cells were called respectively microphages (little phagocytes) and macrophages (big phagocytes) by Metchnikoff, and the term macrophage is still in general use. Large mononuclear phagocytes occur as monocytes in the blood, and as wandering cells in all organs. They line the sinu-

suspension are added particles, such as bacteria or charcoal. A drop of this mixture is placed on a glass slide, covered with a cover slip, and observed on the warmed stage of a microscope.

We may now see two events leading up to phagocytosis. First, the leukocyte moves up to the bacterium or other particle, in a nearly straight line if directed by chemotaxis, or else it encounters the particle by chance while moving at

random. Second, phagocyte and bacterium stick together, and this is essential. If conditions, discussed later, do not permit them to adhere, phagocytosis is impossible.

THE ACT OF PHAGOCYTOSIS.—Small particles, such as single bacteria or grains of charcoal, seem to be ingested in an instant. At one moment they are seen adherent to the outside of the phagocyte, at another moment they are inside. Larger objects such as clumps of bacteria or tissue cells are phagocytized by a more active response of the leukocyte. Liquid cytoplasm is seen to flow around the object in intimate contact with it; that is, the cytoplasm of the leukocyte spreads on the surface of the object until this has been completely engulfed. Apparently, small particles such as single bacteria are phagocytized as the result of simple physical factors such as surface tension, but to ingest larger cells and clumps, additional forces are required, involving gel-sol transformations of the leukocyte.

The Rotating Tube.—For quantitative experiments, the method just described is too complicated, involving as it does amoeboid motion and often chemotaxis on the part of the leukocyte. The method of the rotating tube eliminates these variables.

Leukocytes are suspended in salt solution to which known amounts of unheated serum are added, and then bacteria or other test objects. This mixture is placed in a stoppered glass tube, which is rotated slowly on a wheel, thus keeping cells and particles continuously in suspension. At intervals of time, a drop of the suspension is removed from the tube, spread on a glass slide, and stained. With the microscope, one may count the number of bacteria inside leukocytes, or the number still outside leukocytes, or the percentage of leukocytes that have phagocytized. Thus the course of phagocytosis may be followed and analyzed. With this method, Fenn²⁸ was able to verify his prediction that the number of particles phagocytized would be proportional to the number of collisions expected between particles and leukocytes, as they were mixed by rotation. He also verified the prediction that the number of particles phagocytized would be proportional to the size of the particles. These are the sort of experimental results that would be obtained in nonliving systems. Therefore, phagocytosis, under these experimental conditions, is probably a simple physical process.

Theory of Phagocytosis.—Fenn²⁹ supposed phagocytosis to depend on interfacial tensions between phagocyte, particle, and surrounding serum. When the interfacial tension between particle and

serum is greater than the tensions between particle-leukocyte and leukocyte-serum, the leukocyte is pulled into the particle-serum interface and engulfs the particle. It may happen, however, that the tension at the particle-leukocyte interface is so high that phagocytosis is impossible. The leukocyte is now unable to stick to the particle, as described under the film method of studying phagocytosis, and is likewise unable to spread on a clump of bacteria or a tissue cell.

It is possible to mimic phagocytosis by means of various experiments with nonliving systems.¹⁰² For example, a drop of chloroform is suspended in water, and a bit of clean thread of glass is placed in contact with the chloroform. The glass is not taken up by the chloroform. Then the glass thread is coated with shellac. Since chloroform is able to spread on shellac, the drop of chloroform "phagocytizes" the glass thread, dissolves the shellac, and then ejects the glass thread.

Mechanisms of Phagocytosis.—This experiment with nonliving material emphasizes how important is the surface of the particle that is to be phagocytized. If the surface is sticky or, more precisely, if the leukocyte can adhere to the particle, phagocytosis occurs. Otherwise the crawling leukocyte collides with the particle but, being unable to adhere, merely pushes the particle along, is unable to get hold of it, and so phagocytosis fails.

There are two ways in which the leukocyte's difficulty may be overcome. One is mechanical, "surface phagocytosis."¹⁰⁵ Here the leukocyte forces the particle against a surface, such as the wall of a pulmonary alveolus, so that the bacterium (or particle) is unable to slip away, and therefore is phagocytized. With some particles, however, especially highly virulent bacteria, this mechanism is defeated. For example, type 3 pneumococcus may possess a thick slimy envelope, observable only with an electron microscope,¹⁰⁶ and this envelope, by preventing adequate contact between bacterium and leukocyte, prevents phagocytosis; the bacteria are left free to grow unimpeded by the cellular defenses.

The other way available for conquering this and many other instances of difficult phagocytosis involves an antigen-antibody reaction. Substances (antigens) derived from the bacteria cause the body to form globulins (opsonins) specifically

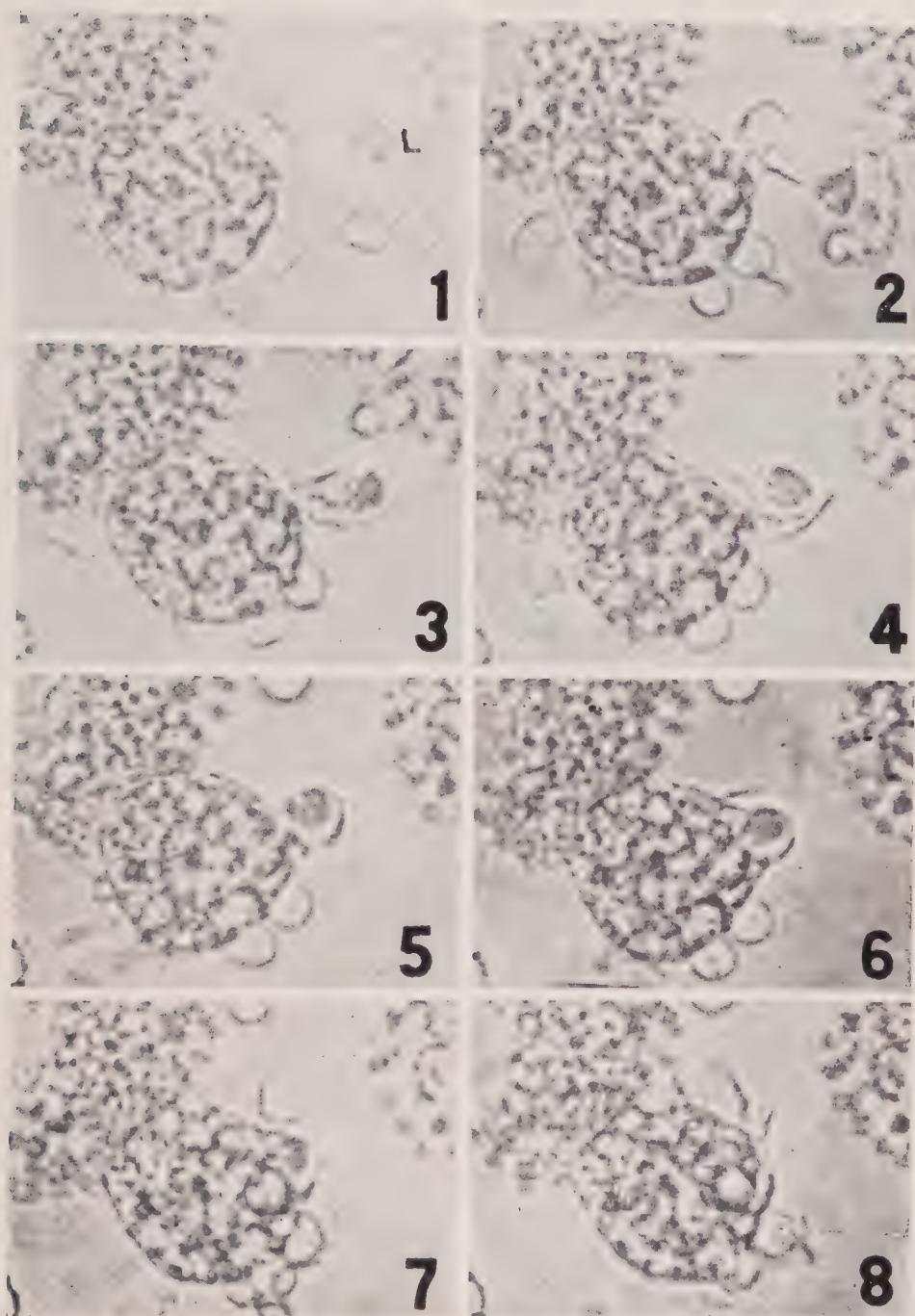


Fig. 19.—Phagocytosis of lymphocyte by a macrophage, from a motion picture of a tissue culture by Dr. W. H. Lewis. Time intervals from 1 to 2 minutes. 1, Lymphocyte (*L*). 2, Macrophage sends out pseudopod toward lymphocyte. 3, Pseudopod envelops lymphocyte and during succeeding minutes gradually draws lymphocyte into cytoplasm of macrophage. ($\times 1,100$.)

effective against the particular kind of bacterium. Uniting with the antigen on the bacterial surface, these opsonins so alter the surface as to enable the leukocyte, whether polymorphonuclear or macrophage,⁶¹ to adhere to and consequently to phagocytize the bacterium. This reaction greatly facilitates and speeds up phagocytosis, and is highly important in overcoming infections. Besides being formed in the body of the host, as just described, the antibody may be obtained in the immune serum of an animal that has been injected with the antigen.

is seen to lie within a vacuole, into which the phagocyte presumably secretes digesting enzymes. Subsequently, the bacterium appears poorly stained and often fragmented. Eventually, after an hour or so, no trace of the microorganism may remain. This is the course of events with most bacteria, such as typhoid bacteria and pyogenic cocci.

FAILURE OF INTRACELLULAR DIGESTION.—Other microorganisms are more resistant to intracellular digestion. This is true especially of the tubercle bacillus. In susceptible individuals, the macrophages

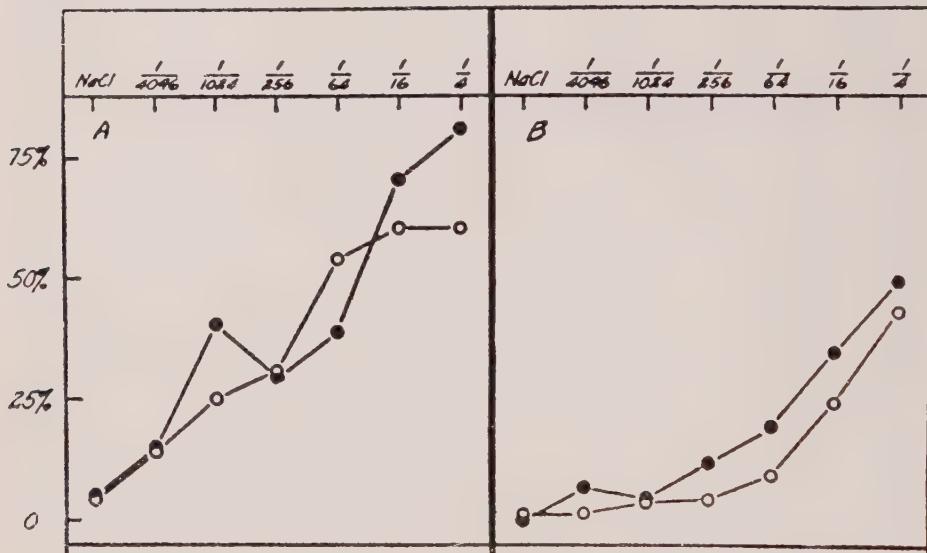


Fig. 20.—Comparative phagocytosis of colon bacillus by macrophages (open circles), and by polymorphonuclear leukocytes (closed circles). Abscissas are increasing concentrations of homologous immune rabbit sera; ordinates show percentages of cells that have ingested colon bacilli. Note the parallelism between phagocytosis by the two kinds of cells.⁶²

Intracellular Digestion.—To be effective in ridding the body of infecting microorganisms, phagocytosis must be followed by intracellular digestion. Most bacteria are readily digested by both polymorphonuclears and macrophages. The course of such digestion may be followed by means of the rotating tube method, described above. From such a tube containing leukocytes and bacteria, a drop of suspension is removed at intervals and spread on a glass slide. When stained and examined with the microscope, bacteria are at first seen well stained and lying within the cytoplasm of the phagocyte. Later, the bacterium

may not only be unable to dissolve the bacteria, but may even fail to prevent their multiplication.⁶⁷ Such macrophages, far from stopping the infection, may actually spread it by transporting bacilli, which later are liberated when the phagocyte dies. In resistant individuals, on the other hand, the macrophages are efficient in digesting and destroying tubercle bacilli.

In kala-azar and leprosy, the parasites are able to live and multiply inside macrophages, which thus constitute their natural host. Thus phagocytosis may prove not to be a defense mechanism but a source of danger to the host.

Conditions Decreasing Phagocytosis.—

In experimental animals, vitamin and protein deficiencies may considerably decrease phagocytosis.^{21, 72} These observations suggest ways in which malnutrition may lower resistance to bacterial infection.

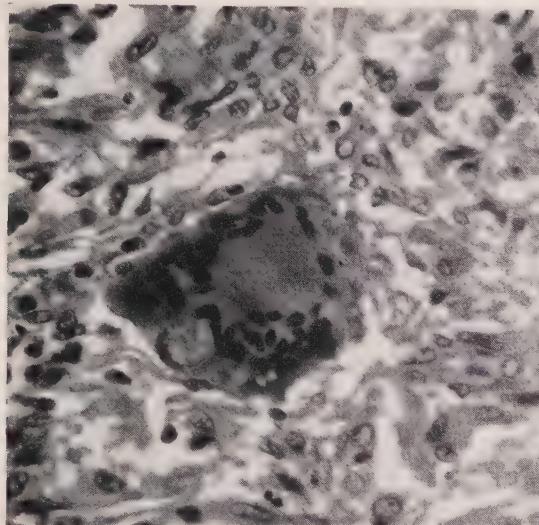


Fig. 21.

Fig. 21.—Phagocytosis of the pathogenic fungus, *Coccidioides immitis*, by a giant cell, in the human lung. The double-contoured organism is seen in the midst of nuclei. ($\times 420$)

Fig. 22.—Failure of intracellular digestion. *Histoplasma capsulatum*, a pathogenic fungus, has multiplied in Kupffer cells of the human liver. The organisms are numerous, small, biscuit-shaped. ($\times 2,100$)

In stained sections of tissue they appear about half again as large as erythrocytes; the cytoplasm is not sharply defined, and even if well preserved does not show the neutrophilic granules distinctly. The granules are best seen in dried blood films stained with Wright's or Giemsa's



Fig. 22.

The Varieties and Functions of Leukocytes

There are three kinds of leukocytes: polymorphonuclears, monocytes, and lymphocytes.* The polymorphonuclears or granulocytes are further subdivided into neutrophiles, eosinophiles, and basophiles, according to the staining qualities of their cytoplasmic granules.

The number of leukocytes in the circulating blood in health ranges from about 5,000 to 8,000 per cubic millimeter. They are distributed approximately as follows, according to percentages: neutrophiles 54 to 73, eosinophiles 2 to 4, basophiles 0 to 1, lymphocytes 21 to 35, monocytes 4 to 8.

POLYMPHONUCLEAR LEUKOCYTES

Neutrophiles are the most numerous and important of the polymorphonuclears.

stain, or one of their modifications; they are small, neither brilliantly red as in eosinophiles, nor blue as in basophiles, but intermediate in color; hence they are called neutrophilic.

Polymorphonuclears arise in bone marrow, through maturation of myelocytes. When immature, the nucleus of polymorphonuclears is unlobed, but as these cells become older, their nucleus becomes lobated, the lobes being connected by filaments. At first the number of lobes is 2, later 3, 4, or 5. It is from this variation in the shape of the nucleus that the cell is called "polymorphonuclear." The immature form is described as non-segmented (nonfilamentous or rod cell); the mature forms are segmented (filamentous). In normal blood, nonsegmented polymorphonuclears make up about 3 to 6 per cent of all leukocytes; segmented forms, about 51 to 67 per cent. But in most acute infections, and espe-

*The plasma cell, the classification of which is uncertain, will be described later.

cially when there is pus in the tissues, immature leukocytes become greatly increased, often constituting 20 per cent or more of all leukocytes. This fact is of great diagnostic importance. The names of Arneth and Schilling are associated with leukocyte counts based on the proportion of immature cells. In such tabulations, the immature cells are customarily enumerated on the left side of the table, the mature forms on the right. Consequently an increase in the proportion of immature forms is called a "shift to the left."

Leukocytosis.—Leukocytosis is an increase in number of circulating leukocytes. The lower limit of leukocytosis varies with the individual, although roughly a count above 10,000 per c.mm. is regarded as constituting leukocytosis, common values falling between 12,000 and 35,000. (See also discussion on page 887.)

Leukocytosis, as commonly used, means an increase in the circulating neutrophiles. As already stated, these cells are increased in most acute infections, while other types of leukocytes are increased only later in these diseases or not at all. Consequently, neutrophiles are increased both absolutely and relatively, and may make up 80 to 95 per cent, or even more, of circulating leukocytes, in place of the normal 54 to 73 per cent.

The significance of leukocytosis is that it is a reaction to injury, especially to infection, by means of which great numbers of leukocytes are brought quickly to the inflamed area. The number of leukocytes available for emigration is greatly increased, and, as fast as they leave the vessels, fresh cells are thrown into the circulation from the bone marrow. Thus untold millions of leukocytes reach an infected area, such as a pneumonic lung, and there attack invading microorganisms. Leukocytosis greatly aids the defense against bacteria and allows the body to utilize to the utmost the processes of emigration, chemotaxis, and phagocytosis.

MECHANISMS OF LEUKOCYTOSIS.—Leukocytosis occurs commonly under two conditions, with acute bacterial infection, burns, and other severe injuries, and after exercise. The mechanisms are quite different.

First, leukocytosis following exercise: As long as the subject is at rest, circulation of blood is not active in all the capillaries. In some the flow is sluggish; in these, leukocytes tend to accumulate. With exercise, blood again flows rapidly through these capillaries and washes the leukocytes out into the general circulation. After violent exercise, such as a running race, the leukocyte count may rise as high as 27,000 or more.⁹⁸ The leukocytes so added to the general circulation are mostly mature.

Second, in leukocytosis occurring in infections, leukocytes are mobilized from the bone marrow by means of two reactions: (1) young leukocytes migrate from the marrow into the blood stream, and (2) more young leukocytes are formed through maturation of myelocytes. Many of the new cells entering the blood stream are immature, and therefore there is a shift to the left, the extent of this shift varying with the degree of stimulation of the marrow.⁸¹ Ordinarily, the least mature cells found in the blood are nonsegmented, but, after excessive stimulation, still less mature forms appear, metamyelocytes and even myelocytes. As already stated, this shift in the blood picture aids one in recognizing the existence of an acute infection.

What stimulates the marrow to make new cells? Before leukocytosis appears, many polymorphonuclears have usually migrated into the infected tissue. Without polymorphonuclear infiltration there is usually no leukocytosis, and probably it is the disintegrated leukocytes in the tissues that stimulate the bone marrow. Products of these cells are presumably absorbed in the inflamed area and carried by the blood stream to the marrow. Several lines of experimental evidence support this view, including the clinical observation that a good way to produce leukocytosis is to inject the patient with leukocytes from another patient. As to the chemical nature of the substance that stimulates the bone marrow, it is, according to Menkin,⁶⁶ a pseudoglobulin.

In migrating from the marrow into the blood stream, leukocytes are thought by some to be responding to chemotaxis; that is, a concentration gradient of an attracting substance is thought to stimulate them to move into the blood vessels.

For this view there is no evidence. Actually we do not understand what causes the leukocytes to move into the blood vessels. Whereas in most acute bacterial infections leukocytosis is the rule, viral infections may cause no change in the leukocyte count. This fact is correlated with the absence of chemotaxis in viral infections, so that granulocytes may be nearly absent from the lesions, and consequently there is no stimulus to the bone marrow.

Leukopenia.—Sometimes there is actual decrease in number of circulating leukocytes, and this condition is known as leukopenia. In influenza and in typhoid fever, leukopenia is the rule. Blood leukocytes may number only 2,000 per cubic millimeter, or fewer. In typhoid fever the bone marrow is damaged, areas of necrosis being found, so that polymorphonuclears cannot be delivered to the blood. In certain infections of the throat, bacterial products are formed that prevent maturation of myelocytes, so the few cells that do enter the blood are immature, even myelocytes themselves.⁸¹ This condition of sore throat with leukopenia is known as agranulocytic angina. (See also discussion on page 889. For leukopenia resulting from radiation, see page 179.)

In typhoid fever and agranulocytic angina, polymorphonuclears are reduced in the blood, and scarce or absent in the lesions. Their work is taken over by macrophages, which appear in greater numbers in typhoid than in other acute bacterial infections, and usually suffice to overcome the invading organisms.

In infections usually attended by leukocytosis, such as pneumococcal infections, leukopenia is ominous, suggesting that the bone marrow is overwhelmed. If an animal is made leukopenic by benzol, it becomes unable to resist pneumococcal infection, even of nonvirulent strains that ordinarily would be easily phagocytized and destroyed; polymorphonuclears are no longer available, and the animal succumbs.⁹⁰

In summary, in diseases ordinarily attended by leukocytosis, moderate leukocytosis is a favorable prognostic sign, whereas leukopenia is unfavorable, suggesting an overwhelming infection.

Functions of Neutrophilic Leukocytes.—Their most important function is phagocytosis. Through chemotaxis, great numbers of leukocytes are quickly brought in contact with bacteria and given opportunity to phagocytize them. In so doing, leukocytes are aided by serum antibodies, either occurring naturally or injected therapeutically. Neutrophiles are too small to ingest most damaged tissue cells, and they are inefficient in phagocytizing carbon, silica, and lipids,⁹² these substances being more efficiently taken up by macrophages. Neutrophiles phagocytize chiefly bacteria, and then digest them by means of intracellular enzymes (discussed on page 38). These are efficient against most kinds of bacteria, but not against tubercle bacilli, which are, however, digested by monocytes.

Neutrophiles constitute the first line of cellular defense, because they can be thrown rapidly and in great numbers into an infected area. Such rapid mobilization depends on a number of reactions already described—leukocytosis, stickiness of vascular endothelium allowing margination, emigration, chemotaxis, and, in addition, these cells are readily available because there are normally great numbers of them circulating in the blood.

Polymorphonuclears are end cells, that is, they never divide nor differentiate further. They are short-lived, probably surviving only a few days. Unless chemotactic substances are continually present to call out fresh polymorphonuclears, their place is taken after a few days by monocytes.

Another function of granulocytes is to digest fibrin and debris in inflamed tissue. This function will be discussed under leukocytic enzymes.

Eosinophiles.—Normally making up only 1 or 2 per cent of circulating leukocytes, eosinophiles may increase to 20 per cent or more. Eosinophilia (i.e., increase in eosinophiles) is found in hypersensitivity of the atopic type (see below), as in asthma and hay fever. Also probably related to hypersensitivity is the eosinophilia excited by animal parasites, especially parasitic worms.¹¹ Eosinophiles emigrate from the vessels and appear in large numbers in the lesions. In asthma they are found in the bronchial secretions and in the sputum. Charcot-

Leyden crystals, often present in the sputum after attacks of asthma, are believed to result from disintegration of eosinophiles. The significance and functions of eosinophiles in hypersensitiveness are not understood. Eosinophilic infiltration is found also in the later stages of many inflammations, as in healing appendicitis and salpingitis, and also in Hodgkin's disease and eosinophilic granuloma.

Eosinopenia (decrease in circulating eosinophiles) may be induced acutely by adrenocorticotropic hormone and by cortisone, and this fact is made use of in gauging dosage of these hormones and in estimating the functional capacity of the adrenal cortex.⁹⁹

Like neutrophiles, eosinophiles exhibit chemotaxis and phagocytosis, though these cells seem to be less efficient phagocytes than are neutrophiles.

Basophiles (Mast Leukocytes).—These have large granules that are stained blue by certain dyes, e.g., alcoholie thionine following fixation by absolute alcohol. The special functions and significance of these cells are unknown. Unlike other granulocytes, they decrease during acute infections. In myelogenous leukemia, however, basophiles may increase enormously, and it is in this condition that they are most conspicuous.

To be distinguished from the mast leukocytes are the tissue mast cells, which are cells of the connective tissue derived from various parent types, and characterized by their basophilic granules. It is especially during chronic inflammation that these cells appear in considerable numbers. There is evidence that they are a source of heparin.²⁷

MONONUCLEAR PHAGOCYTES

These cells are widely distributed, in the blood being known as monocytes, in the tissues as macrophages, histiocytes, polyblasts, clastomacocytes, cells of the reticulo-endothelial system, etc. The great number of synonyms indicates the confusion as to the origins and relations of these cells. Monocytes normally constitute from 4 to 6 per cent of blood leukocytes. Other mononuclear phagocytes occur as wandering cells in tissues of all organs, and, as sessile macrophages, line the sinusoids of liver (as Kupffer cells), spleen, lymph nodes, and bone marrow.

They are abundant in the skin, and omentum, and are the septal cells of the lung. Of the sessile macrophages, the Kupffer cells are especially important as phagocytes because they are extremely efficient in removing foreign particles such as bacteria from the blood, and thereby tend to sterilize it. Under conditions described below, mononuclear phagocytes are transformed into epithelioid and giant cells. In areas of inflammation, monocytes come from the blood, and other mononuclear phagocytes from the adjacent tissues.

Mononuclear phagocytes are found in almost all metazoa. In mammals their appearance and behavior while living may be studied in tissue cultures, e.g., in explants of omentum. When the cells first migrate from the explant they move fairly rapidly, often change shape, and put out both blunt and sharp processes (Fig. 24). They ingest dead cells, bacteria, and debris, and imbibe drops of water.^{53, 53a} Consequently they enlarge greatly and become sluggish or stationary, though their processes continue in motion, and of these the large, petal-like or membranous pseudopods are of special interest, being quite unlike any structure possessed by granulocytes or lymphocytes. In motion pictures these processes are seen slowly waving, and engulfing particles and cells. Like amebae, macrophages may thrust out pseudopods toward nearby objects, surround and draw them into the cell body (Fig. 19). Macrophages are the most efficient of phagocytes, ingesting not only bacteria, but also damaged tissue cells such as lymphocytes or other leukocytes, cells too large to be phagocytized by polymorphonuclears. The appearance of hypertrophied macrophages is shown in Figs. 18 and 26; ingested cells and accumulated fat-droplets are prominent. Subsequently such macrophages may divide and resume active locomotion. In their ability to multiply in the tissues, mononuclear phagocytes differ from polymorphonuclears.

Although in amphibia mononuclear phagocytes show chemotaxis to many substances, in mammals their chemotactic responses seem to be weak. Thus, in explants of rat omentum, macrophages are not attracted by staphylococci or tubercle bacilli, though these bacteria strongly

attract polymorphonuclears.¹⁹ There is some evidence that mammalian macrophages may be attracted over short distances (25 microns) by damaged cells,⁴⁵ and may be weakly repelled by silicates. Generally, however, they appear to move at random, sweeping to and fro, phagocytizing as they go.

In fixed and stained tissues and spreads, macrophages look entirely different from the way they appear in the living state. They are round, with cytoplasm better defined than that of polymorphonuclears, and a little larger. The nucleus is unlobed but often indented, with chromatin uniformly distributed when the nucleus

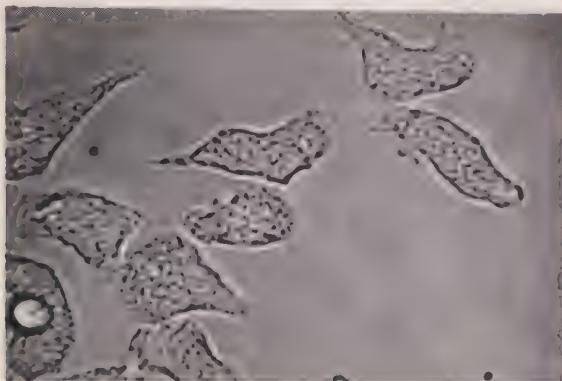


Fig. 23.



Fig. 24.



Fig. 25.

Fig. 23.—Polymorphonuclear leukocytes from the buffy coat of human blood, photographed ($\times 1,100$) while in motion in plasma. (Courtesy Dr. W. H. Lewis.)

Fig. 24.—Small monocytes from intestine of mouse, photographed ($\times 1,100$) while in motion in plasma. (Courtesy Dr. W. H. Lewis.)

Fig. 25.—Lymphocytes from lymph node of mouse. Photographed ($\times 1,100$) while in motion in plasma. Lymphocytes are best represented by 4 cells arranged vertically to right of center of photograph. Observe relatively large, clear nucleus. Large cells with many granules (of fat) are macrophages. (Courtesy Dr. W. H. Lewis.)

is small, but concentrated on the nuclear membrane when cells are hypertrophied. The cytoplasm lacks specific granules, but in tissues usually contains much or little phagocytized material.

In acute infections, mononuclear phagocytes generally appear later in the lesions than do polymorphonuclears, presumably because they are less numerous in the blood and are less chemotactic. Thus they are the second line of cellular defense. However, mononuclear phagocytes may play a decisive part in overcoming an infection, as in lobar pneumonia.⁹² In typhoid fever and in uncomplicated virus infections generally, polymorphonuclears are infrequent in the lesions, so that the burden of combating the infectious agent rests almost wholly on the macrophages.

nuclei, large ill-defined cytoplasm with interlocking processes. Arranged compactly in a tubercle, the cells somewhat resemble epithelium, hence the name, "epithelioid." They occur in several other conditions besides tuberculosis.

Giant cells, i.e., large multinucleated cells, are formed by fusion of many macrophages, and also by amitotic division of the nucleus of macrophages without cell division.⁵² The type of giant cell usually seen in tuberculous lesions is called the Langhans giant cell. The center of this cell is occupied by a granular area, so that the nuclei are crowded to the cell periphery where they are arranged in the form of a horseshoe or circle. Similar cells are met with in other conditions and have

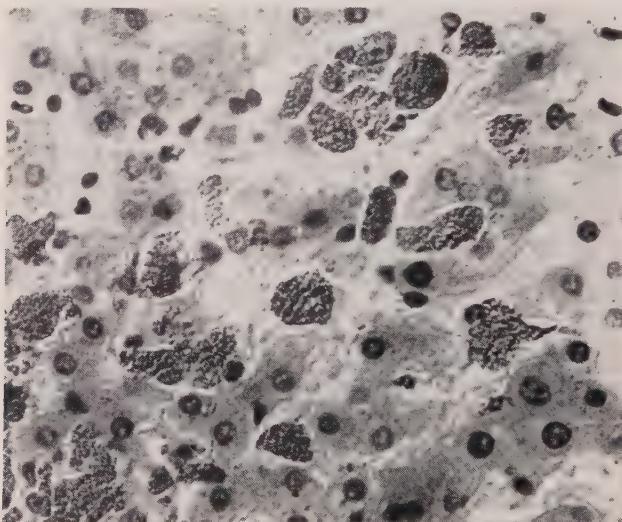


Fig. 26.—Kupffer cells filled with thorium dioxide, which has been injected into the blood stream. Hepatic cells have relatively clear cytoplasm. ($\times 480$)

Acquired immunity to bacterial infections depends in part on the presence of numerous macrophages in the tissues. In chronic infections, it is these cells that play the chief part in cellular resistance. This relation has been studied chiefly in tuberculosis, against which, according to Rich,⁸⁷ macrophages constitute the chief or only defense. These cells phagocytize tubercle bacilli and become transformed into **epithelioid cells**. As the result of stimulation by tubercle bacilli, the macrophages swell and multiply, forming a tissue of cells with large, pale-staining

been observed by Lewis in cultures of normal spleen and lymph nodes.

Another type of giant cell is also formed by macrophages. In this type there is no central granular area, so that the nuclei instead of being confined to the periphery are scattered throughout the cytoplasm. Nuclei may be very numerous, even up to 100 or more. Cells of this type are called foreign-body giant cells, because they are often found about insoluble foreign bodies such as nonabsorbable sutures. Intermediate forms between the two types of giant cells occur.

Functions of Mononuclear Phagocytes.—In addition to the highly important functions of phagocytosis and intracellular digestion already described, and,

theilial blockade. Excessive amounts of carbon or other indigestible particles are injected intravenously, so that macrophages throughout the body become filled

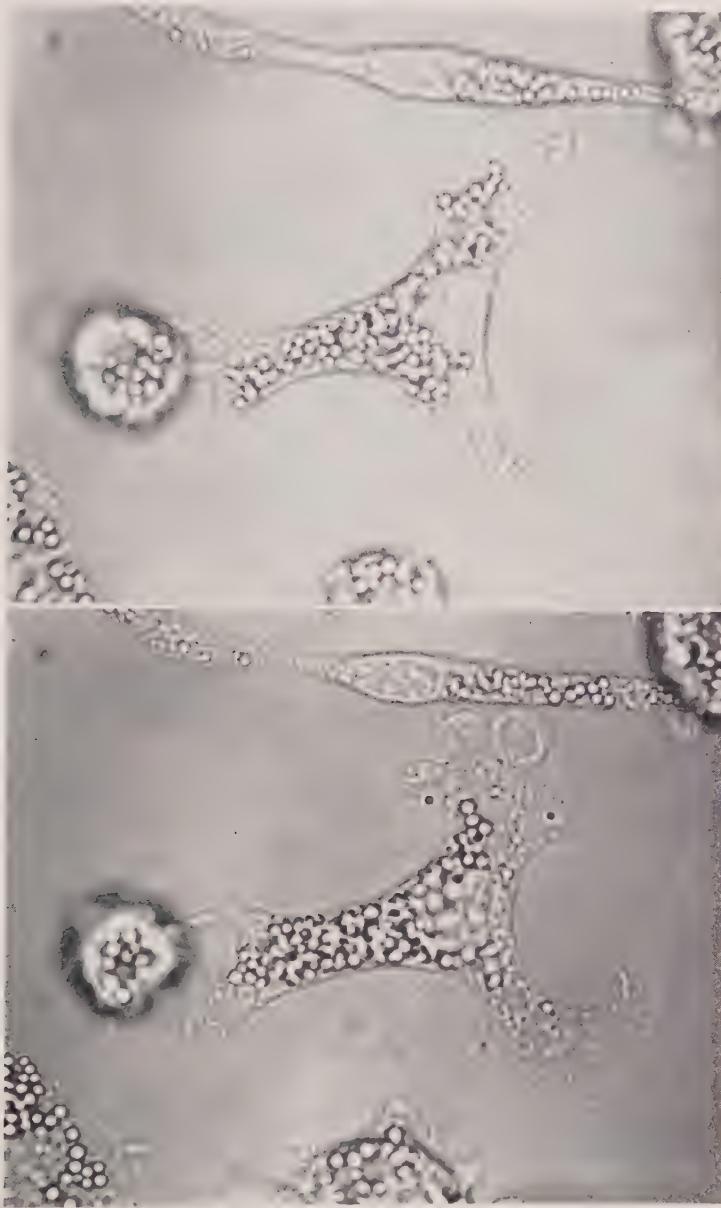


Fig. 27.—Macrophages showing activity of petal-like processes. The two photographs ($\times 1,100$) were taken ten minutes apart. Broad and slender processes which change in size and configuration within the ten-minute interval. (Courtesy Dr. W. H. Lewis.)

enzyme formation (see page 38), macrophages are possibly a source of antibodies.⁴⁶ Evidence for this rests in part on the experiment called reticuloendo-

with these particles, and hence are presumed to be unable to function as producers of antibodies. Following injection of antigens, antibody production is now

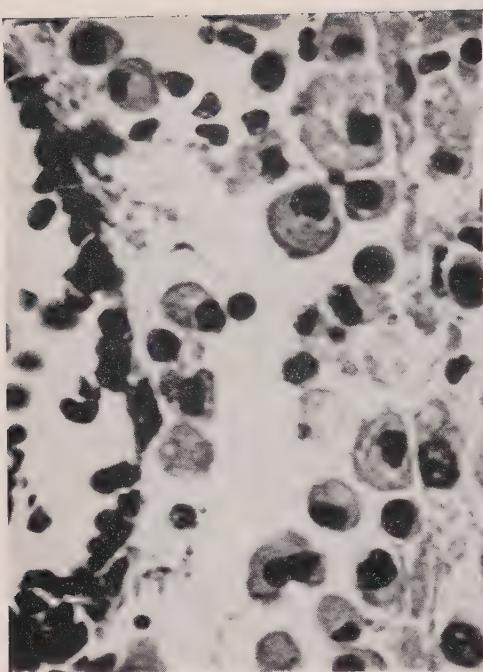


Fig. 28.

Fig. 28.—Infiltration by macrophages, from a pyelonephritic kidney. (Stained with H & E; $\times 850$.)

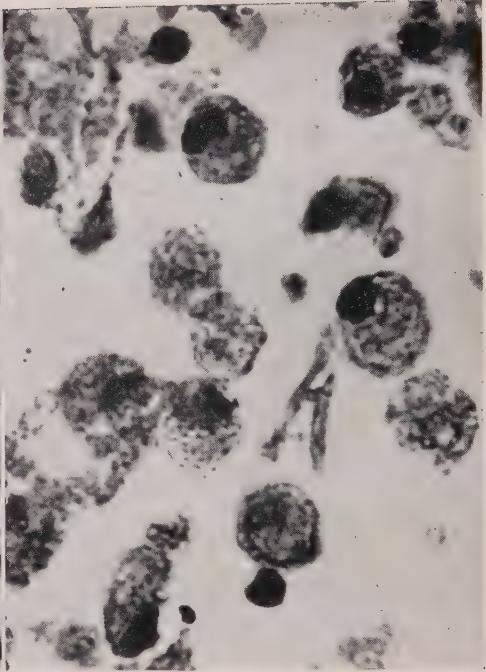


Fig. 29.

Fig. 29.—"Gitter" cells, i.e., macrophages found in areas of softening in the brain. These cells phagocytized damaged cerebral tissue. ($\times 1,100$.)



Fig. 30.

Fig. 30.—Epithelioid cells in a tubercle. ($\times 510$.)

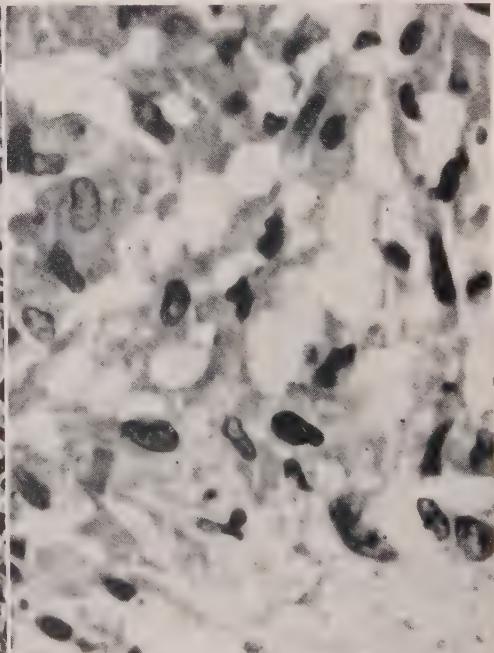


Fig. 31.

Fig. 31.—Epithelioid cells more highly magnified, from a case of sarcoid. ($\times 1,130$.)

found to be delayed. Such experiments suggest that monocytes produce antibodies, but the evidence is not decisive (see also under Lymphocytes below).

Bilirubin is formed from hemoglobin by macrophages in the fixed tissues.⁵⁵

LYMPHOCYTES

The lymphocyte is the third type of blood leukocyte to be considered. It appears later in the course of inflammation than the other types of leukocyte. Lymphocytes reach the tissues by emigrating from blood vessels, just as do other leukocytes,¹⁴ and also by migrating from lymphoid tissue commonly present in most organs.

crease little or not at all in acute infections, though they may increase during convalescence and in such chronic infections as tuberculosis.⁵⁸ (See also under Infectious Mononucleosis, page 888.)

Their mechanism of locomotion is the same as that of the polymorphonuclears,⁵⁴ yet lymphocytes do not exhibit chemotaxis⁶² or, according to most investigators, phagocytosis.⁹⁷ This is the more remarkable because they are so numerous both in the blood and in tissues during inflammation. Especially in chronic inflammation, lymphocytic infiltration is striking, e.g., in the periportal spaces of cirrhotic livers, and in the interstitial

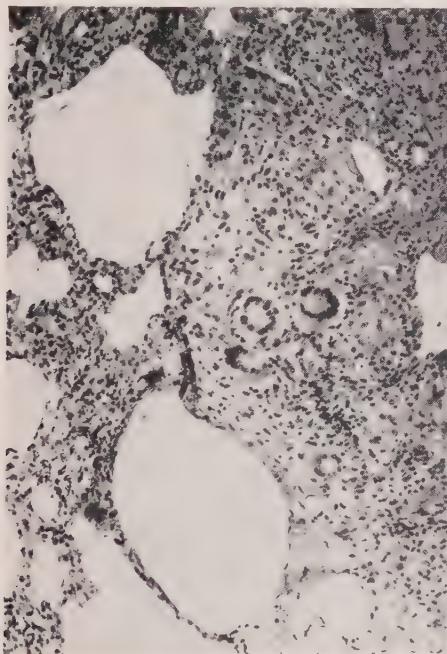


Fig. 32.

Fig. 32.—Giant cells of the Langhans type, from a case of lipoid pneumonia. ($\times 110$)
Fig. 33.—Three giant cells of "foreign body" type. These were formed in response to keratin retained in a hair follicle. ($\times 450$)

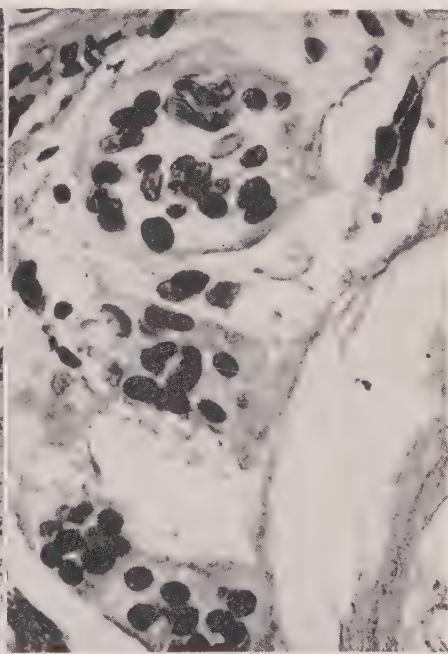


Fig. 33.

As seen in histologic sections, lymphocytes are smaller than polymorphonuclears and about the size of erythrocytes. They appear to consist almost entirely of nucleus, the cytoplasm being scanty. However, in the living cell, the cytoplasm appears distinct and more abundant. In the blood, lymphocytes make up from 15 to 30 per cent of leukocytes, tending to be more numerous in children. They in-

tissue of pyelonephritic kidneys. They form the outside cellular layer of tubercles. They infiltrate the tissues on the edge of tumors and invade tissues transplanted from one individual into another.⁵⁶ They are prominent in the perivascular round-cell infiltration in the brain of syphilis and of various forms of viral encephalitis.

Functions of Lymphocytes.¹⁰⁷—Their great numbers and frequent renewal

(perhaps three times a day) suggest that lymphocytes have very important functions, yet just what these functions are has proved hard to ascertain. Many recent investigations have emphasized the close association of lymphocytes and adrenal cortex. When adrenal cortical extract is injected in experimental animals, great numbers of lymphocytes are

of energy. If confirmed, this function would be of great significance.

Another important function attributed to lymphocytes is production of antibodies. Formerly, macrophages were regarded as the source of antibodies, but according to recent investigations²⁶ the role of these cells, and of granulocytes as well, is limited to phagocytizing and

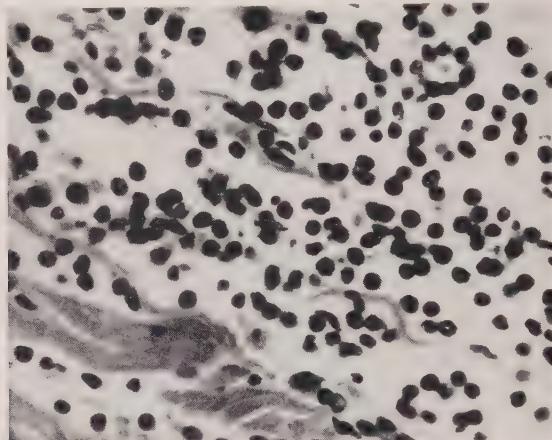


Fig. 34.—Lymphocytes infiltrating connective tissue. In fixed and stained preparations little cytoplasm can be seen. ($\times 510$.)



Fig. 35.—Lymphocytes in motion. The two dumbbell-shaped cells near the center were moving in directions corresponding to the upper corners of the photograph. Explanted from a lymph node. ($\times 1,100$.) (Courtesy Dr. W. H. Lewis.)

dissolved within three to six hours.²² Similar changes may occur spontaneously in man following injury such as may be caused by trauma, burns, or infection, which bring about discharge from the pituitary of adrenocorticotrophic hormone and, from the adrenal, of cortical hormone, and thus lead to dissolution of lymphocytes. Protein thus liberated is thought to serve as an emergency source

digesting cells and particles containing antigen. Thus antigen may be made available in soluble form that is usable by lymphoid cells in forming antibodies. (See also under Plasma Cells below.)

Evidence that lymphoid cells may form antibodies rests upon such experiments as the following²³: When antigen, such as bacteria, is injected into the foot, regional lymph nodes enlarge, lymphoid

cells increase in number and release specific antibody (gamma globulin) into the efferent lymphatics in high concentration. Such experiments show that antibodies are formed in lymphoid tissue, as do other types of experiment, e.g., whole body irradiation with x-rays causes rapid atrophy of lymphoid tissue and correspondingly delays formation of antibodies. One of the most important lymphoid organs in producing antibodies is the spleen.

Among other functions attributed to lymphocytes should be mentioned their ability to invade and destroy transplants of tissue (including tumors) from animals of the same species.¹⁰⁰ (See below under Skin Grafting and Transplantation of Tissues.)

posed are monocytes and primitive connective tissue cells.^{70, 71}

Recent evidence suggests that plasma cells, too, form antibodies.^{25, 107} Thus there is good correlation between appearance of antibodies during experimental immunization and hyperplasia of plasma cells in lymph nodes and spleen. Also, antibodies can be extracted in high concentration from tissues rich in plasma cells.

Small round-cell infiltration is a term applied to collections of cells resembling lymphocytes, seen in chronic inflammation, such as the perivascular infiltrations of the brain in syphilis. The term applies to the round shape of the nucleus. Some of the cells are lymphocytes, some plasma cells, and others connective tissue cells.

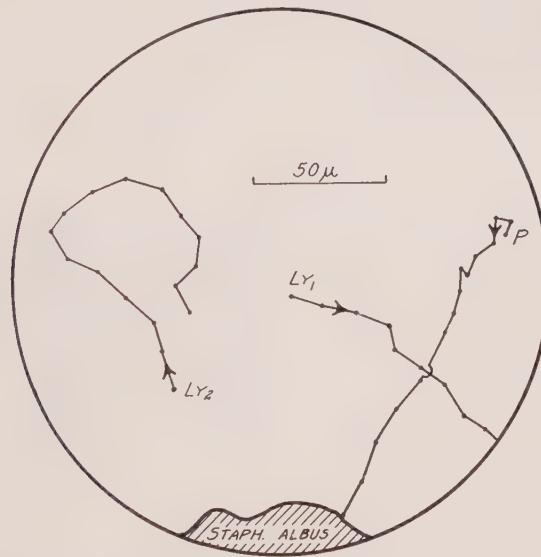


Fig. 36.—Absence of chemotaxis in lymphocytes (Ly^1 , Ly^2) in contrast to positive chemotaxis in polymorphonuclear leukocyte (P). Camera lucida drawing of paths of these cells as observed in a spread of human blood. The lymphocytes are seen to have moved at random whereas the granulocyte moved almost directly toward the clump of *Staph. albus*.

PLASMA CELLS

The plasma cell, like the lymphocyte, is found in chronically inflamed tissues. Its cytoplasm is larger than that of the lymphocyte and is basophilic. The eccentric nucleus often has its chromatin arranged in a pattern suggesting the spokes of a wheel, and is surrounded by a pale area of cytoplasm.

The plasma cell is often regarded as derived from the lymphocyte, but this is not certain; among other origins pro-

The term is a noncommittal one, used when we are unable to specify just which cells are present.

Another origin for small round cells has been suggested by Clark,¹⁶ from his observations on the same cells, day after day, in transparent chambers implanted in the rabbit's ear. He has followed the gradual transformation of polymorphonuclears from active to stationary cells, till they appear identical with small round cells seen in fixed tissues.

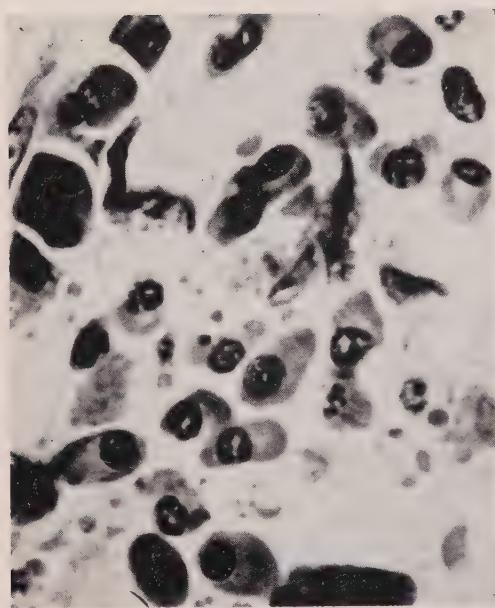


Fig. 37.—Plasma cells have an eccentric cartwheel nucleus with an adjoining clear area. (The large cells are macrophages.) ($\times 1,070$.)

LEUKOCYTIC ENZYMES

Leukocytes contain a variety of enzymes which vary in the different types of leukocytes and from one species to another. These enzymes are concerned chiefly with intracellular processes, such as digestion of phagocytized material. The enzymes of greatest interest in the study of inflammation are the proteases of polymorphonuclears. These are active only within the cell till the leukocyte dies.⁷⁷ Then trypsin and cathepsin (the enzyme causing autolysis) escape into the tissues. Trypsin is liberated in large quantity by polymorphonuclears of man.⁴² But at the same time as trypsin is liberated, a trypsin-inhibiting substance passes from the blood vessels with the exudate into tissue spaces, so that, in most inflammations, trypsin is inactivated and does not digest tissues. Thus, in inflammation of pleural, peritoneal, and other serous surfaces, there is usually abundant serous exudate, and consequently no tryptic digestion of tissues. The same is usually true in pneumonia: resolution occurs without destruction of lung tissue, in typical cases. When, however, a strong irritant (such as staphylococci or streptococci or, experimentally, turpentine) acts on the

solid tissues, in which there is little room for serous exudation, great numbers of neutrophiles accumulate in a confined space and there liberate trypsin in high concentration. The result is suppuration and local dissolution of tissue—in other words, an abscess. Resolution can no longer restore tissues to normal, and healing occurs with scarring.

An important function of leukocytic enzymes is digestion of fibrin and debris in inflamed areas, for undigested fibrin acts as a foreign body and leads to fibrosis, such as occurs, for example, in unresolved pneumonia. It is not definitely known which enzymes are responsible for dissolving the fibrinous exudate. As the proteolytic enzyme of polymorphonuclears is active chiefly in alkaline medium, whereas the reaction of inflamed areas is often slightly acid, and also because this enzyme is inactivated by serum, it may play little part in resolution. Macrophages liberate a protease active in acid medium, and this may help dissolve the exudate in later stages of acute inflammations that are nonsuppurative.



Fig. 38.—Perivascular round-cell infiltration of the brain. From a case of lethargic encephalitis. Probably most of the cells are lymphocytes. ($\times 130$.)

Enzymes of lymphocytes, in those species in which they have been studied, are less powerful than those of polymorphonuclear leukocytes.⁵

THE CHEMICAL MECHANISM OF INFLAMMATION

At the beginning of this chapter it was stated that inflammation is a reaction to injury. It has long appeared probable that injury releases from cells and tissues some substances that induce inflammatory responses of blood vessels. Thus, Ebbecke²⁴ proposed that something is released by stimulated cells that causes vasodilatation and pain. Lewis⁵⁰ added that this substance sets up axone reflexes and increases vascular permeability leading to exudation. As Lewis was able to elicit these reactions by injecting histamine, he suggested that the substance released from stimulated or injured cells is histamine or else some substance with histamine-like effects. This he called "**H substance**," i.e., histamine-like substance. According to present evidence,¹⁰¹ histamine may be responsible in part for inflammatory redness (erythema, flare) but probably not for increased capillary permeability or cellular migration.

Another active substance was recovered from exudates produced in the pleural cavity of dogs by Menkin,⁶⁵ who dubbed the substance leukotaxin. He believed it to be a peptide. On injection into the skin it increases capillary permeability (e.g., to trypan blue) and also causes emigration of leukocytes.

Peptides with similar effects have been prepared from proteolytic digestion of serum albumin, fibrin, and other proteins.⁹⁵ Since these properties are not shared by proteins or amino acids, it appears established that various peptides can reproduce the exudative phenomena of inflammation. These substances are believed to be formed by proteases in serum or cells, acting on blood or tissue proteins, at sites of tissue injury. Bacteria also, since they possess both proteins and proteases, are presumed to form peptides directly, and these, in contact with tissues, cause inflammation.

The Cardinal Signs of Inflammation.—These, as already mentioned, are redness,

heat, swelling, and pain. What are the mechanisms of these changes, in the light of present knowledge? These signs may all be immediately caused by products of cellular injury.

Redness is the result of dilatation of blood vessels, and of filling of previously collapsed capillaries. It results from direct stimulation of capillaries and from widening of arterioles mediated by axone reflexes. **Heat** is the result of the same mechanism. Hyperemic skin, such as that over a carbuncle, is warmer than normal skin, but not warmer than rectal temperature.²⁰ Increased metabolic rate of inflamed tissues plays a negligible part in the increased heat. **Swelling** comes in part from increased blood in the area, but far more from exudate, both plasma and cells. **Pain** in inflammation is probably caused by the action of products of injured cells upon sensory nerve endings. Whether the effective substance is histamine⁹³ or not⁵¹ is unsettled. In addition, the increased tension due to exudate in the tissues may be a cause of pain. Other factors that have been thought to cause pain are increased numbers of potassium and of hydrogen ions in inflamed tissue, and local increase in osmotic pressure resulting from breaking up of large molecules into a number of smaller ones.

TYPES OF INFLAMMATORY LESIONS

A great variety of pictures are found in inflammation, both as seen with the naked eye and with the microscope. Differences in the picture depend, first, on the type of tissue. The gross appearances, especially, vary from organ to organ, depending on peculiarities of structure. Second, the picture varies with the particular agent to which the tissue is reacting. The skin, for example, reacts to the virus of herpes simplex by forming a blister, to staphylococci commonly with an abscess (such as a boil), while to streptococci it may react with a diffuse type of inflammation known as erysipelas. Consider the remarkable difference in appearance of the lung according to whether it is reacting to pneumococci in lobar pneumonia, or to tubercle bacilli, with a chronic process characterized by cavitation and fibrosis.

When we analyze the pictures of inflammation found in any organ, we find that they depend largely on predominance of one of three processes: exudation, proliferation of tissue cells, or necrosis caused by the injurious agent.

vessels into the lesion. We speak of (a) **serous** exudation when the exudate resembles serum (that is, consists of water, solutes, and albumin from the blood) but fibrin and leukocytes are scanty. A serous exudate is often encountered in

Fig. 39.

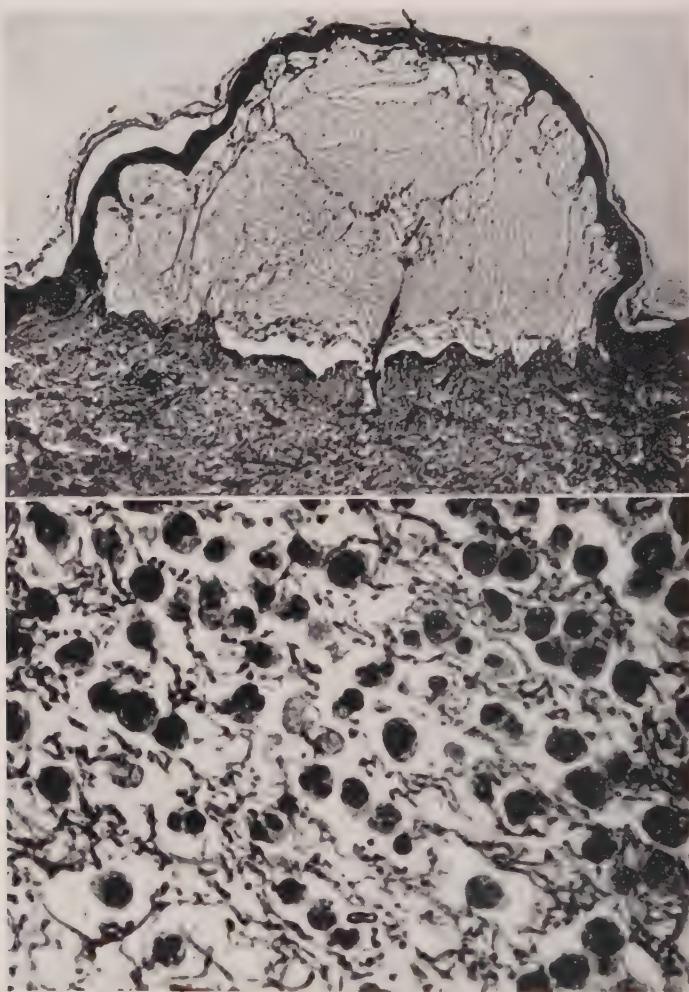


Fig. 40.

Fig. 39.—Fibrinous exudate in blister of human skin following application of cantharides. ($\times 30$.) (Courtesy Dr. F. D. Weidman.)

Fig. 40.—Fibrinocellular exudate from a case of pneumococcic meningitis. Granulocytes and macrophages lie in meshes of fibrin. ($\times 760$.)

These three processes are combined in different proportions and so produce complex pictures. Examples will be given in which one or other of the three processes predominate.

1. **Exudation.**—Here the dominating process is escape of fluid or cells from the

tuberculous pleurisy, in which several liters of liquid may accumulate in the pleural cavities. **Serous inflammation** is a concept, originated by Rössle,^{92a} of a relatively noncellular reaction of connective tissue to injury. As the result of vascular damage, often of undetermined

nature, a serous fluid rich in protein escapes from capillaries and causes edema of the surrounding connective tissue.⁸² If long continued, such edema leads to sclerosis of the affected organ without round cell infiltration and without previous formation of granulation tissue, which in other types of inflammation precedes the development of scar tissue. Examples of lesions allegedly so arising are rheumatic nodules in the heart (q.v.) and hepatic cirrhosis in hyperthyroidism. However, many pathologists do not accept such pathogenesis of these lesions.

Fibrinoid degeneration, often conspicuous in lesions of rheumatic fever, rheumatoid arthritis, and disseminated lupus erythematosus may be related to serous inflammation.³ (See Fig. 340, page 453, and Fig. 342, page 455.) Chemical changes in the ground substance of connective tissue, especially increase in hyaluronic acid and other mucopolysaccharides in the rheumatoid diseases is being investigated.⁶⁹ Of special interest is the action of cortisone in decreasing serous exudation, e.g., of the joints, in the rheumatoid diseases; the antagonistic action of hyaluronidase to cortisone is being studied.⁴⁴

In a (b) **fibrinous** exudate, the content of fibrin is high, as in plasma. For example, a fibrinous exudate is found in lobar pneumonia, and in pneumococcal pericarditis; the serous membrane is covered with an adherent layer of fibrin, which may be peeled off with tissue forceps. With the microscope, a fibrinous exudate is seen to consist largely of eosin-staining fibrin threads, at first separate but after a few days becoming condensed into compact masses. Fibrinous exudates result from greater increase in vascular permeability than do serous exudates, as the fibrinogen molecule is relatively large. In the lung, fibrinous exudates are caused especially by pneumococci.

(c) A **purulent** exudate consists of pus. Here it is neutrophiles that predominate. An example is empyema of the pleural cavity.

Often the characters called serous, fibrinous, and purulent are mixed, so that one speaks of serofibrinous or fibrino-purulent exudates. When an exudate contains many erythrocytes, so that it

appears red, we speak of a **hemorrhagic exudate**. A common example is hemorrhagic cystitis.

2. Proliferation.—In some inflammatory lesions, proliferation (that is, multiplication of cells) predominates. Though cell proliferation is often inconspicuous in acute inflammations caused by bacteria, a notable exception is found in the lymph nodules early in typhoid fever; these show great multiplication of macrophages. Viruses have peculiar ability to stimulate cell division, so that the early stages of many virus diseases show conspicuous proliferation.⁹¹ This is well seen in the skin, where epithelial proliferation is found in smallpox, vaccinia, chicken pox, and herpes simplex. See Fig. 436, page 559, showing proliferation of capsular epithelium in subacute glomerular nephritis, forming a crescent, or demilune.

In bacterial infections, proliferation is more evident in the subacute and chronic stages. Thus in the tubercles of tuberculosis, the lesion consists largely of proliferated macrophages, here known as epithelioid cells. In chronic inflammations generally, proliferation regularly dominates the picture. It is especially connective tissue cells that multiply. This will be discussed under Repair and Chronic Inflammation (pp. 49-60).

3. Necrosis.—Although necrosis occurs, at least in individual cells, in all inflammations, it sometimes dominates the picture, as in gas gangrene. In this infection the tissues may be discolored and have a foul odor, while, microscopically, fragmentation of nuclei, or their failure to stain at all, gives a typical picture of necrosis. Leukocytes are scarce. Necrosis here results from action of toxins produced by members of the genus *Clostridium*. Other organisms such as the spirochetes of Vincent are often associated with necrotizing types of inflammation. In still other instances, necrosis may result not from bacterial toxins but from obstruction of blood vessels, as is probably often the mechanism in gangrenous appendicitis.

Exudation, proliferation, and necrosis are combined in various ways and in different locations to produce well-known types of inflammation. Brief descriptions of these types follow:

Catarrhal Inflammation

Catarrhal inflammation is a type of inflammatory reaction found in mucous membranes. Catarrh means "a running down," and refers to the discharge from these surfaces when inflamed, e.g., the

dropping from the nose in the common cold. Such catarrhal inflammations are characterized by excessive mucous secretion, by an exudate at first serous, later mucopurulent, and by desquamation of the surface epithelium. It is character-

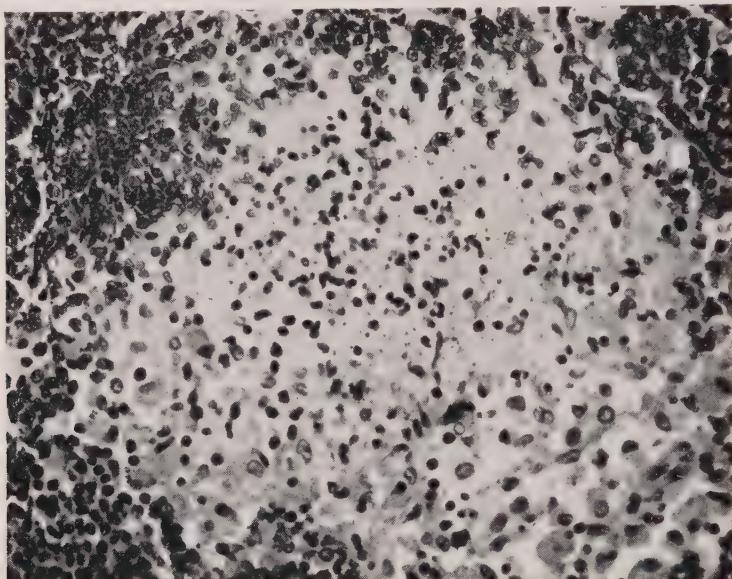


Fig. 41.—Necrosis in inflammation. The necrotic area in the center of the tubercle contains many nuclear fragments. Epithelioid cells are seen at the periphery. ($\times 760$.)

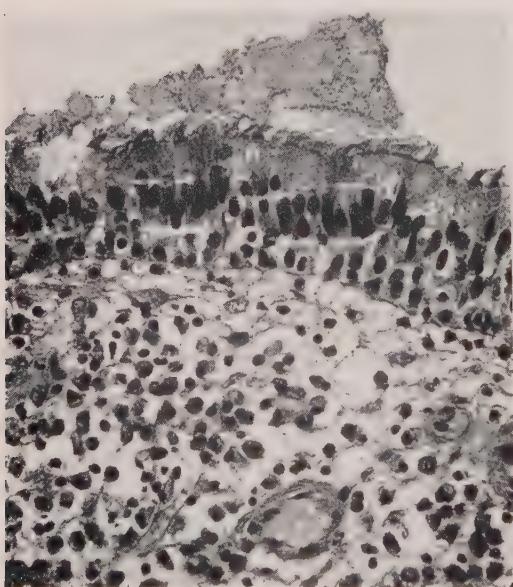


Fig. 42.—Catarrhal inflammation in a nasal polyp. The tissue is edematous and infiltrated with leukocytes. Observe the mucous secretion beyond the ciliated epithelial cells at top of photograph. ($\times 350$.)

istic of catarrhal inflammations that deeper tissues are little involved, the changes being confined to the superficial tissues.

Pseudomembranous Inflammation

Pseudomembranous inflammation is a response of mucous surfaces as in the pharynx, larynx, trachea, bronchi, and intestines, to a powerful necrotizing agent, e.g., the toxin of diphtheria bacilli and irritant gases. The surface epithelium is destroyed, allowing the irritant to penetrate the deeper tissues, where it increases permeability of the vessels. Consequently, plasma exudes from these vessels and spreads on the eroded surface, where it coagulates, enclosing necrotic epithelium in its fibrinous meshes. This network constitutes the false membrane characteristic of this type of inflammation.

Ulcer

Ulceration means loss of substance from the surface of an organ, with inflamma-

tion of the adjacent tissue. In the pathogenesis of such a lesion, necrosis occurs as the result of toxins or other poisons, or from inadequate blood supply, and then the necrotic area becomes loosened and separated from the living tissue. A frequent site of ulceration is the alimentary canal. Intestinal ulcers are a regular feature of typhoid fever, of intestinal tuberculosis, and of both bacillary and amebic dysentery. In chronic leg ulcers, disturbance of circulation is an important factor. Ulcers occur in many locations and from many causes; they are among the commonest and most important inflammatory lesions.

rather than diffusely spreading. To produce an abscess, bacteria must first penetrate the tissues, either through a wound or through a hair follicle, causing a boil or, in pyemia, as emboli from the blood. When bacteria have thus established themselves, the tissues react by pouring out great numbers of polymorphonuclear leukocytes. These become so concentrated in the injured area that they liberate large amounts of trypsin, and this overcomes the tryptic inhibitor of the serum, which is able to infiltrate the compact solid tissue only in limited quantity. Consequently, trypsin digests damaged



Fig. 43.—Ulcer of stomach extending through the muscularis. The bed of the ulcer is formed by scar tissue, and similar fibrous tissue is observed in the thickened submucosa, giving evidence of a long-continued process. ($\times 8$.)

Abscess

An abscess may be defined as a collection of pus in solid tissue. Such a lesion is caused by an irritant of great intensity, such as staphylococci or, experimentally, turpentine; and it is characteristic of such an irritant that it remains localized

and dead tissue and converts it into the semiliquid material known as pus.

Thus, an abscess consists of a central collection of pus surrounded by inflamed tissue heavily infiltrated with polymorphonuclears. As long as the irritant (e.g., staphylococci) persists, more leukocytes

are attracted, fresh pus is formed, and more tissue liquefied. During digestion of tissue, large molecules are split into smaller ones, osmotic pressure is increased, and consequently more water is attracted from the surrounding tissue. The result is that pressure increases in the abscess, often causing pus to burrow through the tissue, following lines of least resistance, such as septa between muscles. Eventually the pus reaches a surface and is there discharged. Burrowing and erosion

rather is absorbed, or, if too abundant, may remain as sterile fluid (a cyst), or becomes thickened, dried out, eventually surrounded by a fibrous tissue capsule and so remains permanently; or perhaps eventually the former abscess is calcified.

Phlegmonous Inflammation

A phlegmon is, like an abscess, a lesion of solid tissues. But whereas an abscess is circumscribed and has a wall, a phlegmon is diffuse, without definite limit.

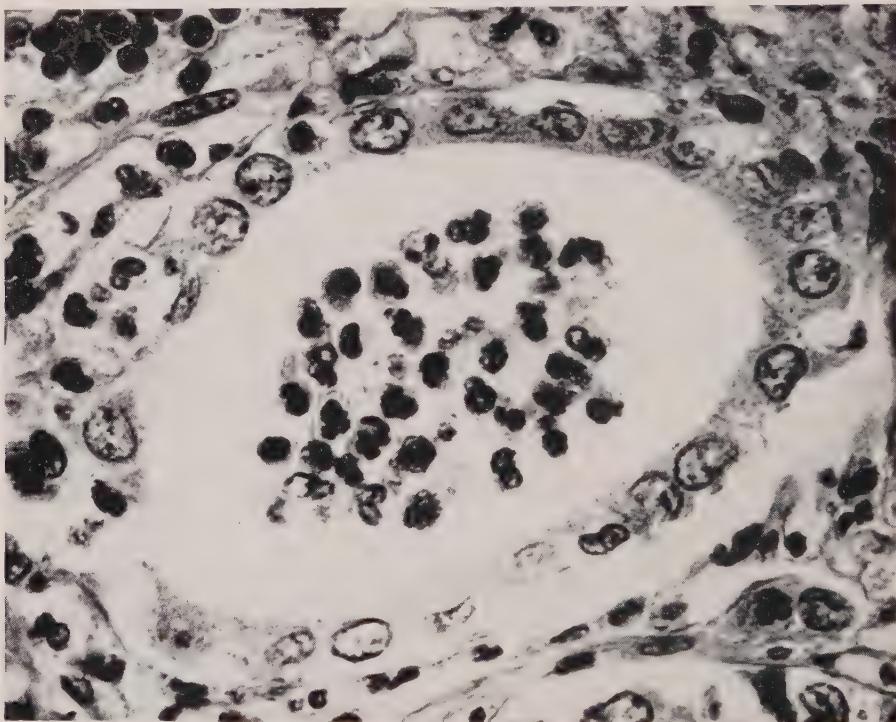


Fig. 44.—Pus cells (degenerated polymorphonuclear leukocytes) in a renal tubule from a case of pyelonephritis. The lobes of nuclei may still be distinguished. ($\times 850$.)

cause considerable damage, which the surgeon seeks to prevent by opening the abscess to establish free drainage. Thus the irritant is removed and healing begins. Suppuration, i.e., formation of visible pus, involves destruction of tissue, and is therefore an irreversible process, one that cannot be restored to normal by resolution but rather heals with scarring. The healing process is described below.

At other times the irritant is destroyed by body defenses before pus burrows to a surface. Pus then no longer forms, but

The reason for this difference is that the irritant, especially streptococci, is not contained in one place, but tends to scatter through the tissue. Correspondingly the exudate is scattered. Thus, in appendicitis, one finds leukocytes and fibrin separated by bands of muscle fibers, and infiltrating through the entire thickness of the organ. Erysipelas is another example of phlegmon. In such lesions, leukocytes, being widely scattered, may now here be in sufficient numbers to cause suppuration.

Fig. 45.

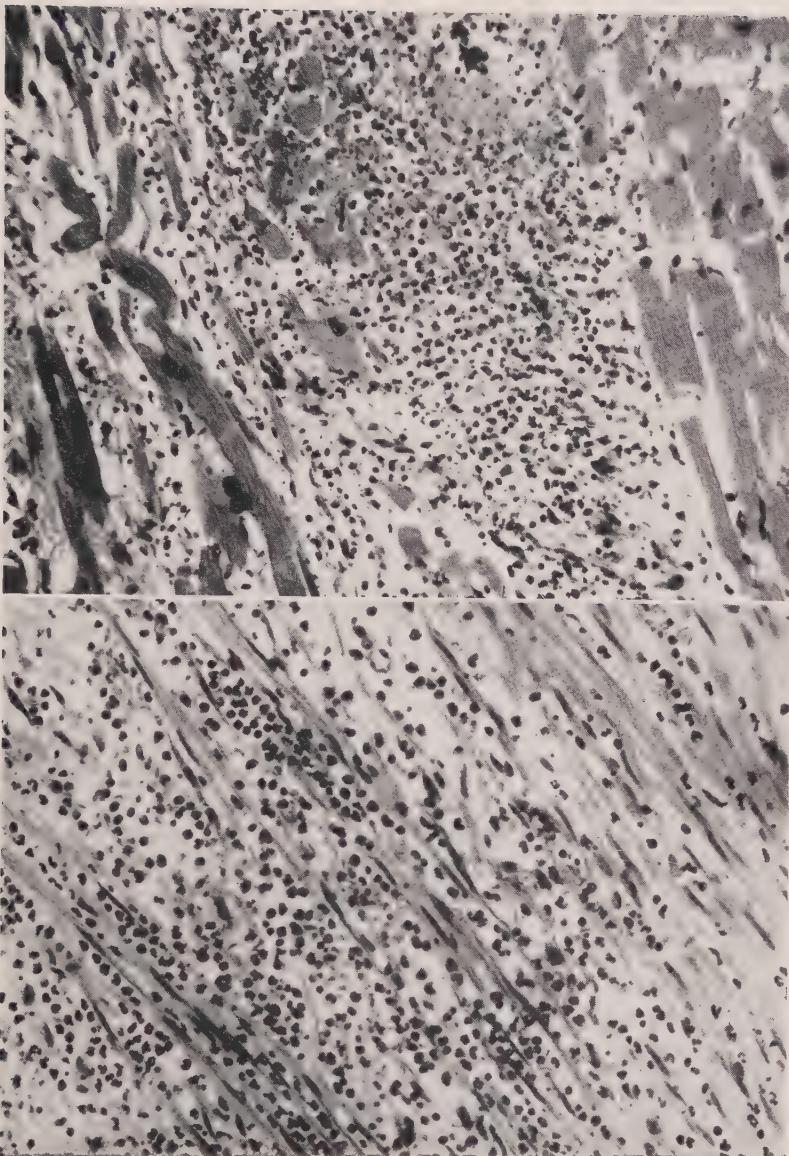


Fig. 46.

Fig. 45.—Small abscess of myocardium. A local collection of pus cells has replaced muscle fibers, of which undissolved fragments are seen near the edge of the lesion. ($\times 370$.)

Fig. 46.—Phlegmon of appendix. Fibers of the muscularis are separated by exudate in which many polymorphonuclear leukocytes are recognizable. The lesion is not circumscribed. ($\times 270$.)

ALLERGIC INFLAMMATION (HYPERSENSITIVENESS)⁸⁶

Arthus Phenomenon⁷⁹

If horse serum is injected into the skin of the rabbit, there is little local reaction. But if horse serum is injected first intra-

venously and two or three weeks later into the skin, a violent local inflammatory response ensues, with great heat, redness, and swelling. So intense is the reaction that often the vessels become thrombosed; they rupture with many small hemorrhages, and, as result of ob-

struction of blood vessels, the skin may be deprived of its blood supply and may undergo necrosis and ulceration.

This is an example of **allergic inflammation**. Some foreign substances, especially proteins, cause no injury or inflammation the first time they enter tissues; but the second time, injury and inflammation may be intense. The tissue cells have been sensitized by the first exposure, and thereafter they are hypersensitive. Their reactivity has been altered. That is the meaning of the word **allergy**.

The explanation is as follows: The foreign protein (here horse serum) acts as an antigen (allergen) and excites formation of antibody (reagin). The antigen disappears, but the antibody remains and is fixed on tissue cells. When antigen is next introduced into the tissues it unites with antibody,⁷⁸ this union apparently occurring on certain tissue cells. The union is of such an explosive nature that the cells are injured, and release substances that cause vascular dilatation, hemorrhage, thrombosis, and increase in vascular permeability.

In man, asthma and hay fever are diseases of this nature. Patients afflicted by them have become sensitized to foreign proteins such as ragweed pollen, epithelium of horses, certain food proteins, or one of a host of substances. When ragweed pollen is inhaled in the autumn it combines chemically with antibody already present. If the reaction occurs in the bronchi, an attack of asthma results, with spasm of the bronchial muscle, so that the patient can scarcely breathe; if the reaction is in the nose, hay fever is the consequence.

Antibodies are present also in the blood of susceptible persons, and can be demonstrated by passive transfer (Prausnitz-Küstner). In this test the patient's serum is injected into the skin of a normal person, and later the antigen into the same spot. If an inflammatory reaction results, it is taken as evidence that the antigen was responsible for the patient's hypersensitivity.

This type of hypersensitivity is known as the atopic type. It is characterized by its familial incidence, by eosinophilia, both of the blood and of the bronchial and nasal mucosae, and by antibodies in the serum, as already described.

Periarteritis nodosa and rheumatic fever have long been thought to have a basis of hypersensitivity, and Rich and Gregory⁸⁹ have recently produced lesions resembling those found in each of these diseases by repeated injections of horse serum into experimental animals. Glomerular nephritis is another disease in which hypersensitivity probably has a part.

When tuberculin (killed tubercle bacilli) is injected into the skin or conjunctival sac of an individual never infected with tuberculosis, the resulting inflammatory reaction is minimal. But in an individual having or having had tuberculosis, redness and swelling appear at the site of injection after a few hours (positive tuberculin reaction). This is the bacterial or tuberculin type of hypersensitivity (**bacterial allergy**).

This type of hypersensitivity differs in several ways from the atopic type. It appears not at once but after a number of hours. Antibodies cannot be demonstrated in the blood. There is no eosinophilia. Necrosis of cells results not from thrombosis and loss of blood supply, as in the anaphylactic type, but from direct action of antigen on mesenchymal cells. That such is the fact is demonstrable in tissue culture of mesenchymal cells from tuberculous animals⁸⁶; tuberculin added to such a culture kills the cells, whereas cultures from nontuberculous animals are unharmed. In contrast, cultures from tissues sensitized to nonbacterial proteins are not harmed by addition of the antigen.

It is probable that the tuberculin type of hypersensitivity, like the anaphylactic type, depends on an antigen-antibody reaction, though this is disputed. Hypersensitivity may be important in the pathogenesis of tuberculosis and syphilis, and may be the cause of caseation necrosis in these diseases.

Any pathogenic bacterium or virus may cause hypersensitivity. Thus, a child vaccinated against smallpox for the first time shows no reaction until the third or fourth day, and the vesicle does not reach its full development until the twelfth day. But on subsequent vaccination, redness appears within twenty-four hours and the vesicle is fully developed in three days.

In summary, the inflammatory response to the antigen develops more rapidly in

hypersensitiveness and is of greater intensity than in the absence of hypersensitivity. Vascular permeability is increased to a greater extent, there is more inflammatory edema, greater emigration of leukocytes, and often an earlier appearance of macrophages.

REGENERATION AND REPAIR

Up to this point we have studied such local tissue reactions as neutralize, isolate, or destroy injurious agents. It remains to describe how the damaged tissues are restored. This is done through: (a) removal of exudate and dead cells, which, as we have already learned, are phagocytized, or dissolved by action of enzymes, and (b) through replacement of lost cells by new ones.

If the new cells are similar to those they replace we speak of *regeneration*, while *repair* is a broader term that includes replacement either by cells and tissues of the same kind as those lost, or of a different, often simpler kind.

Regeneration

Regeneration has already been noted as one of the primitive reactions to injury, occurring in protozoa and metazoa, as well as in man, though less well developed in higher animals than in most of the lower ones. Replacement of lost cells by new ones occurs not only after injury but, in some tissues, such as epidermis and blood, continuously, as old cells wear out. This is known as physiological regeneration.

There is, however, great variation in the ability of different kinds of cells and tissues to regenerate. The supporting tissues regenerate well. Thus connective tissue (collagenous, reticular, and elastic) is formed by connective tissue cells called fibrocytes. New bone is laid down by osteoblasts, cartilage by chondroblasts, adipose tissue by lipoblasts. Blood vessels are readily regenerated, new capillaries arising from endothelium of surviving capillaries, while muscular and connective tissues in veins and arteries are formed by other cells of the mesenchyme.¹⁰³

Epithelium, too, regenerates well, and this is true not only of the epidermis of the skin but of glandular epithelium such as that of the gastrointestinal tract, liver,

and kidney. Cyclic regeneration of uterine mucosa and of mammary glands occurs normally. New cells always arise from pre-existing cells which have retained the ability to revert to embryonal appearance and functions: they enlarge, become round, and undergo cell division until lost tissue has been replaced. Then they reassume the character of adult cells.

Other kinds of cells, however, in post-embryonal life, lose this ability to regain their embryonal character and, consequently, to regenerate. These are the more highly specialized cells such as muscle and nerve cells. Smooth muscle, e.g., in intestine and uterus, regenerates poorly, being replaced by scar tissue. Skeletal muscle fibers, when injured, may be able to regenerate lost sarcoplasm, but are unable to form new muscle cells. As to cardiac muscle, there is no convincing evidence of its regeneration. Nerve cells, too, whether in the central nervous system or in ganglia elsewhere, are unable to divide and to replace lost cells. Nerve fibers, however, can be replaced, provided that the nerve cell survives. Thus, certain highly evolved cells retain little or no power of regeneration. When these cells are lost, they are replaced by tissue of simpler type, usually connective tissue, or, in the central nervous system, by neuroglia.

Atypical Regeneration.--Complete restoration of a damaged organ depends not only on the ability of its parenchymatous cells, such as epithelium, to regenerate, but also on the degree of damage to the supporting tissues. If these are destroyed, regeneration of the organ is likely to be atypical. Thus, in the skin, if only epidermis is lost, restoration is usually complete, but if corium is lost as well, sweat and sebaceous glands are not reformed nor are the papillae. Consequently, the new skin is smooth; the fingers, for example, lack the loops and whorls familiar in the fingerprint.

The liver is often the site of extensive necrosis and regeneration. If the sinusoids and reticular structure are not destroyed, the lobules may be perfectly reformed by multiplication of surviving hepatic cells. Such complete regeneration may occur in infectious hepatitis.⁵⁹ If, however, the framework of the lobule is destroyed, as in hepatic cirrhosis, newly



Fig. 47.—Atypical regeneration of skin. The right side of the photograph shows approximately normal skin, with papillae and epidermal ridges. On the left side, regenerated epidermis is thin and smooth, papillae have failed to regenerate. ($\times 90$)

formed tissue is not arranged in lobules; central veins are lacking, and portal triads are buried in scar tissue.

Regeneration of Organs.—Ability to replace lost organs or parts of organs is less well developed in man and other mammals than in many more primitive animals. In certain worms, the head may be regenerated from segments cut from the middle of the body.⁴³ Adult salamanders may be able to grow a new tail, while their larvae can, in addition, replace lost extremities.

In mammals, the liver has great power of regeneration. Rous and McMaster⁹⁴ removed about seven-tenths of the liver in rats, and observed complete restoration in weight. When the portal branches to part of the liver are occluded, that part atrophies, but the rest of the liver makes good the loss. This it does by cell division, the cells increasing the length of liver cords and the size of lobules.

In the lung, also, lost tissue may be replaced. In rats, all but one lobe may be excised, with restoration to the original weight.¹⁷ To what extent new alveoli are formed, or pre-existing ones enlarged, is not known. Loss of one kidney causes considerable enlargement and increased functional capacity of the surviving one.

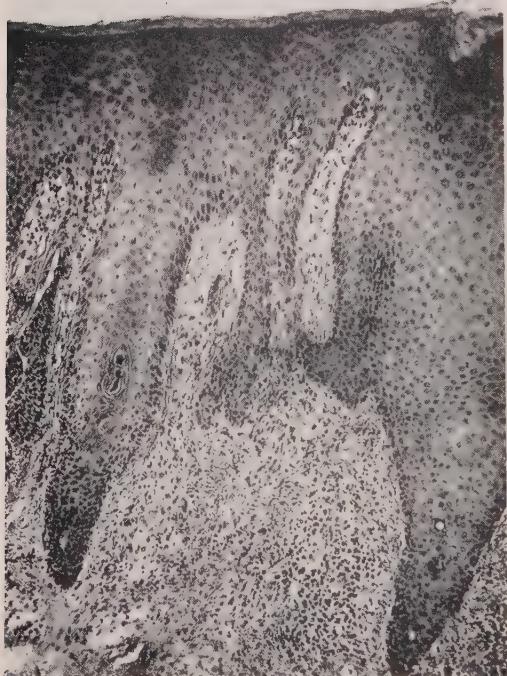


Fig. 48.—Excessive regeneration of epidermis, in the edge of an ulcer of the skin. Corium contains numerous "inflammatory cells." (Courtesy Dr. F. D. Weidman.)

No new nephrons are formed; rather, the nephrons already present enlarge. Glomeruli are unable to regenerate, but tubules may be completely restored following necrosis of many of their cells. Testes, ovaries, and adrenals enlarge slightly to moderately, after removal of the opposite organ.² When the spleen is removed, accessory spleens when present may increase to many times their previous size.

Repair⁴

By repair is meant replacement of damaged or destroyed cells and tissues, either by regeneration of cells similar to those lost, or by dissimilar, often simpler, cells. Repair follows every injury, whether due to infection, burning, trauma, or other agent. The repair processes may begin within a few hours of injury, and therefore overlap in time the vascular and leukocytic reactions already described.

RÉPAIR OF WOUNDS OF THE SKIN

Repair will be described as it occurs in wounds of the skin because these have been most studied, but the processes involved are similar after injuries of every kind, e.g., healing of ulcers, repair of tuberculous cavities, of abscesses in liver or kidney, or after trauma to deeper parts by missiles.

Crust Formation.—After hemorrhage has ceased, the wound is covered with coagulated blood, which dries and hardens into a crust or scab. The crust is useful in two ways: it stops leaking of fluid from injured tissue and it forms a barrier against infection. Thus the crust effects provisional closure of the wound.

Crust formation is possible only if blood is available and if conditions permit drying. These conditions are met best in wounds of the skin, or in wounds of deeper tissues if the clotted blood is exposed to air. In the cornea, however, no blood is available to form a clot. During repair of uterine mucosa following menstruation, conditions do not permit drying of blood. In these and other tissues, closure is brought about by cell migration, as will be described.

Removal of Dead Tissue, Other Debris, and Exudate.—When, as the result of injury, a large mass of dead tissue remains in contact with living parts, the dead tissue may be removed by sloughing.

There occurs inflammation of the surrounding living tissue, and the processes of repair form a line or zone of demarcation between tissue that is living and the dead mass, which constitutes the slough. As the result of repair, the slough loses continuity with the living tissue and so is removed.

Smaller amounts of dead tissue, as well as debris and exudate, are removed by liquefaction and phagocytosis, as already described. Liquefaction of dead cells is produced largely by enzymes liberated by the dead cells themselves, though leukocytic enzymes probably aid. Leukocytes of all kinds move into the clot and the damaged tissue.

REPLACEMENT OF LOST CELLS AND TISSUES

Replacement of lost cells and tissues is accomplished by two processes, cell migration and cell proliferation. In wounds of the skin, the cells chiefly concerned are fibrocytes, vascular endothelium, and epithelium. These types of cell have the property, on appropriate stimulation, of swelling and reassuming their embryonal appearance; they become actively motile and undergo mitotic division.

Fibrocytes (Fibroblasts).—These probably arise from cells already present in connective tissue, that is, from connective tissue cells. These cells enlarge and migrate from surviving tissue into the clot, where they have been preceded by polymorphonuclears and monocytes. In studying the migration of fibrocytes, a useful technique is the transparent chamber set in the rabbit ear.⁵⁶ Under these conditions, fibrocytes appear large, elongated, and provided with processes; they move in straight lines with a velocity of about 8 microns per hour. As fibrocytes move into the clot, they appear bipolar, but later they put out processes in various directions, and these processes fuse with those of neighboring fibrocytes. Between the cells fine fibrils develop, increase in number, and coalesce to form larger fibrils of collagen.⁵³ These lie extracellularly in parallel rows, between which are found the now shrunken cells; they become mature connective tissue cells, and lie dormant until stimulated to renewed activity. The fibers laid down in this way form sheets of collagen, and several such sheets may be formed one on an-



Fig. 49.—Fibrocytes have elongated nuclei, with chromatin concentrated mostly in the nuclear membrane and nucleoli. The cells with oval nuclei are plasma cells. ($\times 880$.)

other. The direction in which the fibers of each sheet are oriented is determined by the tensions to which they are subjected.

After fixation and staining, fibrocytes, as compared with monocytes, have a less sharp and clear outline. In the nucleus, the chromatin is concentrated along the nuclear membrane and in one or two nucleoli. Whereas the macrophage in inflammatory tissue commonly contains phagocytized cells and debris, the fibrocyte is generally not phagocytic.

Endothelium.—While fibrocytes are migrating, changes appear in the capillaries at the edge of the wound. Here the endothelial cells swell and divide, thus forming a bud that projects from the capillary and then begins to migrate. The path of migration is not, however, a straight line, such as is followed by fibrocytes, but rather an arc of a circle. Following this curving path, the endothelial cells meet other similar cells also traveling in an arc, and the two fuse, forming a loop that is attached to capillaries at both ends. At first the loop is

solid, but later becomes hollow; that is, it develops a lumen into which blood flows from the parent capillaries. In this way a new capillary is formed. The process is repeated, new loops being formed as endothelial cells migrate farther and farther into the clot. Thus a new tissue is built, known as **granulation tissue**, so called because it appears to the naked eye to be composed of pink granules. These granules consist of (1) newly formed capillary loops, (2) fibrocytes, (3) leukocytes. It is granulation tissue that fills up the defect in a gaping wound.

Granulation tissue has noteworthy properties: (1) it bleeds freely if even slightly traumatized, as by gentle rubbing with gauze; (2) it is insensitive, lacking nerves; (3) it is resistant to infection, because it contains many mononuclear phagocytes.³³

Epithelium.—The cells of the epiderm are firmly attached to each other, and consequently the epithelium of the skin migrates as a sheet of cells, in contrast to fibrocytes which migrate separately. The mechanism of locomotion of this epithelial sheet appears to depend on ameboid motion of its constituent cells.

In order to migrate, epithelium requires a substratum of mesenchyme. If the mesenchyme remains intact, epithelium may begin migrating at once. Thus in wounds of the cornea limited to the epithelial layer, these cells move in from the sides and may close the defect in as short a time as six hours. Closure is here accomplished solely by cell migration; cell division plays no part. The same is true of closure of small wounds of the skin.

If, however, the mesenchyme has been disrupted, as in deep wounds of the skin, epithelium is unable to migrate until a new mesenchymal substrate is built up by granulation tissue. Thus occurs a delay of several days, after which epithelium spreads on the granulation tissue, passing between this and the scab. It is noteworthy that epithelium spreads not on top of but beneath the scab, and therefore in contact with the newly formed mesenchyme. As the epithelium moves into the wound from all sides, the advancing edges meet and fuse and thus

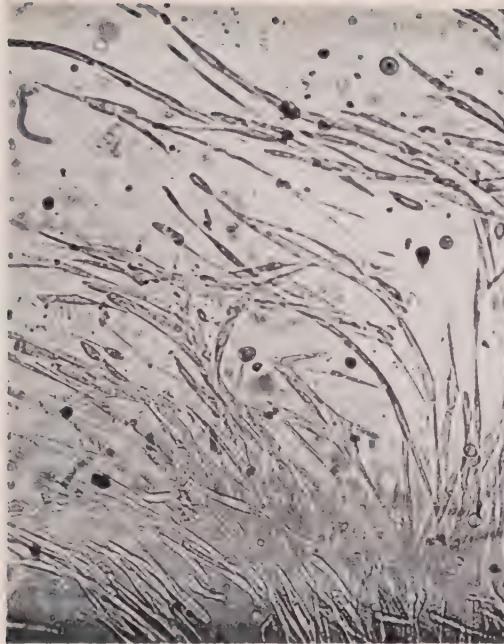


Fig. 50.



Fig. 51.

Fig. 50.—Fibrocytes in tissue culture grow as separated cells. (Courtesy Dr. D. R. Coman.)
Fig. 51.—Epithelium in tissue culture. Epithelium grows as a sheet of cells. (Courtesy Dr. D. R. Coman.)

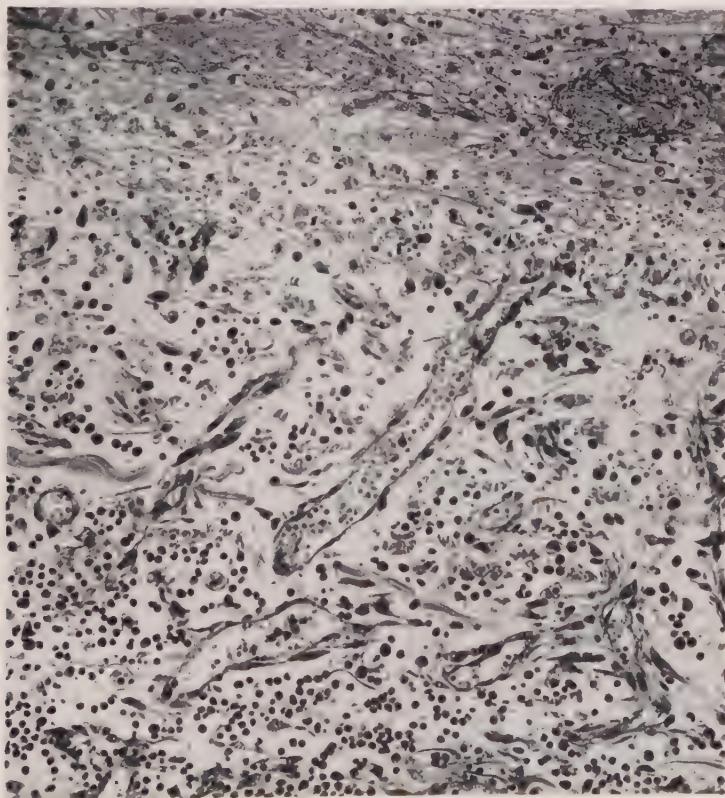


Fig. 52.—Granulation tissue from a case of pericarditis. Below the center are seen several newly formed capillaries, separated by loose connective tissue, in the interstices of which lie inflammatory cells. At top of photograph, above the mesothelial lining (not easily distinguishable) is fibrinous exudate. ($\times 170$.)

close the wound permanently. The scab, which had effected provisional closure, then drops off.

Cell division aids migration in replacing epithelium lost in extensive wounds. Of course, even in normal epithelium, mitosis occurs, as old cells must continually be replaced by new ones. After a wound, mitosis appears at first to be depressed, and in the initial stage of migration there may be no cell division. Later, especially in larger wounds, mitoses become abundant. In experimental wounds they have been observed to be twice as numerous as in resting skin.⁷ Also, cell division may continue after migration has ceased with the closure of the wound, until all the cells lost have been replaced.

of granulation tissue fades progressively, until there is left a white, shrunken, often depressed and distorted area, the scar.

Adhesions are commonly formed in repair of injury to the pleura, pericardium, joints and peritoneum, i.e., serous surfaces. During inflammation, e.g., peritonitis, both visceral and parietal layers become covered with fibrin. This is often not completely removed during repair, because leukocytes and their enzymes are not sufficiently concentrated. Fibrin on the visceral and parietal surfaces sticks together and forms a bridge. During repair, fibrocytes migrate across this bridge and lay down collagen, which becomes a permanent adhesion. Later, such an adhesion may be seen as a white ribbon on

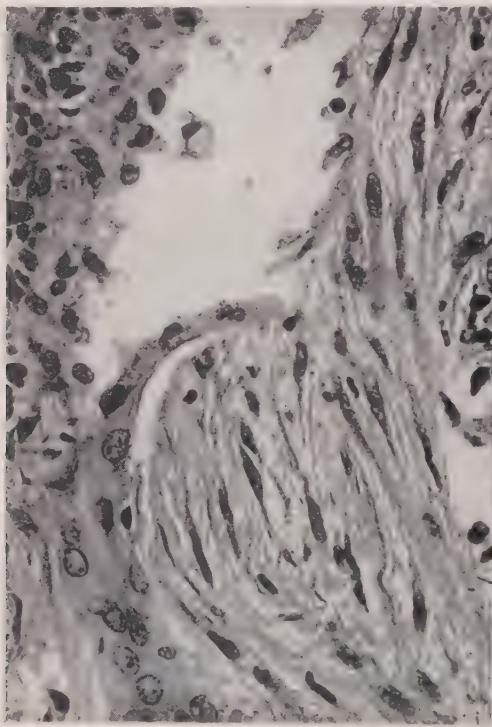


Fig. 53.

Fig. 53.—Scar, early stage. Connective tissue cells lie parallel, are bipolar, provided with processes, are separated by extracellular collagen fibers. ($\times 370$.)

Fig. 54.—Scar (late stage) in cirrhotic liver. The scar is composed largely of collagen fibers with scanty elongated nuclei of connective tissue cells. ($\times 180$.)

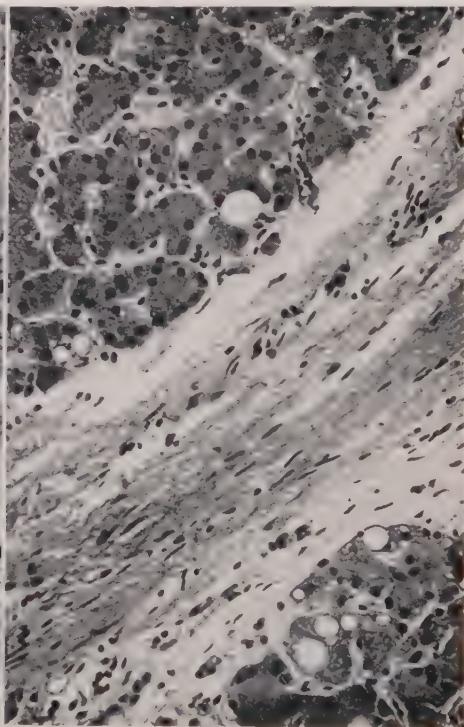


Fig. 54.

Cicatrization means the conversion of granulation tissue into a scar. The collagen fibers recently formed by fibrocytes undergo shrinkage, while many capillaries regress and no longer contain blood. As these capillaries disappear, the red color

the peritoneum and may catch and constrict the bowel, causing intestinal obstruction. Adhesions may unite parietal and visceral layers completely, causing the pleural cavity to be obliterated, as sometimes occurs after extensive pleurisy;

this commonly does little harm. If the pericardial sac is obliterated, little harm is done unless the scar tissue so shrinks or is so dense as to interfere with filling of the heart in diastole; this seriously interferes with cardiac function. In the joints, adhesions are crippling, and may cause fixation.

Types of Wound Healing.—Repair is said to be primary where the edges of the wound are in apposition; secondary, if the wound gapes.

Primary repair occurs under several conditions.

Again the wound is closed by spreading of epithelium. A few leukocytes migrate into the blood clot, injured capillaries regenerate, a few connective tissue fibers are formed by fibrocytes, and healing occurs practically without scar.

3. If sufficient elastic and muscle fibers are cut, the edges of the wound retract; but the surgeon may be able to bring them together with sutures, and, if so, primary repair occurs as described in the preceding paragraph.

4. When the entire thickness of epidermis is lost, as by abrasion, superficial vessels of the corium are injured and

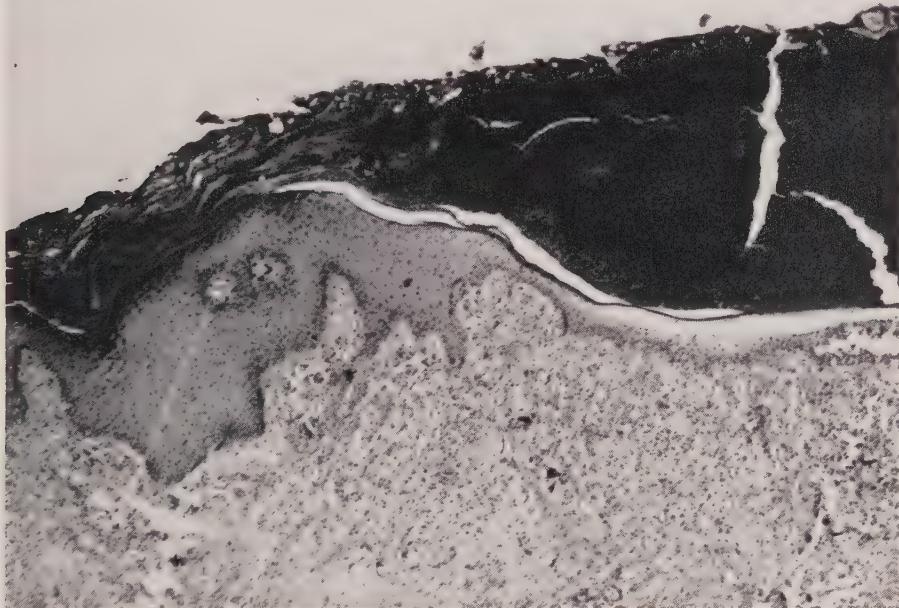


Fig. 55.—Healing under a crust (dark mass at upper right). Epidermis is approximately normal on left, but under the crust has been lost and has incompletely regenerated from surviving epidermis at left. ($\times 37$.)

1. The wound is so superficial as to involve only the epiderm, the corium remaining uninjured; hence there is no bleeding. Repair is accomplished merely by migration of epithelial cells until they meet each other across the cut. Such a wound may be repaired in one day.

2. The wound, e.g., a cut made by a knife, is deeper and enters the corium, where blood capillaries are cut and a few drops of blood escape. There is practically no retraction of the wound edges, and the blood sticks the edges together.

bleed, but the corium remains otherwise intact. The escaped blood coagulates to form a crust, under which epiderm spreads and closes the wound. This type of repair is called *healing under a crust*. No scarring results.

Secondary repair occurs when the wound edges cannot be approximated, because too much tissue has been destroyed. The defect is gradually filled by granulation tissue, on which epithelium migrates until it covers the defect. As granulation tissue regresses, it leaves a scar.

Stages of Wound Closure.—Carrel and Hartmann¹² studied rate of closure of skin wounds, both experimental ones and those in man. The outline of the wound was traced on cellophane, and the area was measured with a planimeter. In this way the closure of the wound was followed day by day. Several stages are recognizable.⁴

1. *A latent period*, lasting from one to several days, during which the size of the wound does not change.

2. *A period of contraction*, during which the edges of the wound are pulled together, probably from shrinkage of granulation tissue. The rate of contraction is proportional to the size of the wound and is most rapid at first, decreasing in rate as the wound edges come closer. Either contraction may continue until closure is complete, or it may cease while the wound edges are still some distance apart.

3. *Epidermization*, that is, the spread of epidermis over granulation tissue. This process begins later than contraction and continues until closure is complete. However, if contraction ceases when the edges of the wound are more than 20 to 25 mm. apart, epidermization becomes slow and may cease entirely. This is an important consideration in treating wounds; extensive loss of epithelium may require skin grafting, in order to obtain complete epithelial covering.

Skin Grafting and Transplantation of Tissues.—Skin grafting is a frequent surgical procedure undertaken to speed healing, prevent infection, prevent crippling and unsightly scarring, and stop the loss of proteins from oozing of serum—a factor of great importance after extensive burns. We are here concerned only with “free” grafts, that is, pieces of skin entirely removed from their original site and vascular supply. Free grafts are used in various thicknesses; e.g., the Thiersch graft consists only of epithelium and tops of papillae; the split-skin or intermediate graft includes also the upper layers of the corium, while the full thickness graft includes all the layers of corium. In addition, many small pieces of thick skin may be grafted close to one another (Reverdin or pinch grafts). Various modifications in technique were developed during World War II.

The biological problems encountered in skin grafting are those of transplantation in general, the principles of which have been set forth by Leo Loeb⁵⁷ in his important work on *The Biological Basis of Individuality*.

Loeb has shown that when tissue is transplanted from one part to another of the same individual (*autotransplant*), the graft generally succeeds, its cells mostly survive, there is only

slight reaction of the tissues receiving the transplant, and the transplant is soon vascularized by the surrounding tissue. When, however, tissue is transplanted from one individual to another of the same species (*homotransplant*), the result is different. After a few days there is local lymphocytic reaction of the tissues about the transplant, with accompanying blood lymphocytosis, and these cells invade the transplant. Fibrocytes react strongly and surround the graft with abundant connective tissue. In addition, the transplant is poorly vascularized, and so dies.

If the transplant is taken from a close relative of the recipient (*syngenesiotransplant*), the reaction is intermediate between those just described. The transplant may at first appear to be successful, but after a few weeks it dies. Only when the graft is transferred from one identical twin to the other is success permanent.

Still greater incompatibility is apparent when tissue is transplanted from an individual of different species (*heterotransplant*). Now the first cells of the host to react are the polymorphonuclears, which invade the transplant, and there is also blood leukocytosis. Later, the lymphocytes may react. The transplant dies within a few days.

Failure of homotransplants and heterotransplants to survive permanently is generally attributed to development of immunity against foreign cells.⁵⁸

Recognizing these principles, surgeons use autotransplants rather than homotransplants whenever possible. However, homotransplants are also widely employed. Thus, permanent success has been achieved in homotransplantation of the cornea.⁶⁴

Bone grafts³² from another individual are used with such success that “bone banks” have been established in medical centers. Although the transplant does not survive, it serves as scaffolding or trellis for deposit of new bone, also probably serving as a source of calcium. The transplant is removed bit by bit by osteoclasts, while at the same time new bony trabeculae are formed, this replacement being known as “creeping substitution.” Skin, too, is transplanted from person to person, especially to effect temporary closure of large burns, though the transplant eventually sloughs.⁸

How does the skin graft “take”? When a skin graft is applied to a raw surface or one covered with granulation tissue, the two surfaces become stuck together by fibrin, which exudes from the recipient tissue (and may be supplemented by fibrin film added by the surgeon). Such temporary adhesion may be completed in about five hours.⁸⁰

The success of the graft now depends largely on vascularization of the transplant by recipient tissues. During the first few days the vitality of the transplant must be maintained by plasma which exudes from the surrounding tissue into the transplant. But, already, new capillaries have grown into the fibrin clot and thence into the transplant, where they make connections with the capillaries of the transplant, and so vascularize it. Vascularization may be completed in about eight days. At the same time, fibrocytes migrate from the surrounding tissue, and bring about fibrous union. Many of the

cells of the transplant show degenerative changes, but dead cells are replaced by regeneration of surviving cells, rapidly in the case of epithelium, more slowly in the corium.

Besides skin and bone, cartilage and tendons are frequently transplanted during the repair of wounds, and the same principles apply.

Factors Influencing Rate of Healing.—Carrel found that an important factor in the healing of wounds is the age of the patient, wounds healing faster in the young than in the old. From Carrel's data, du Noüy²³ derived an empirical equation which relates the age of the patient and the size of the wound with the time required to heal. Given the patient's age and the size of his wound, it is possible to predict the course and termination of healing, under standard conditions; and conversely it is possible to derive the patient's age from the size of the wound and rate of healing. This equation allows one to evaluate the effect of treatment, in hastening or prolonging the healing process.

An important factor in influencing the rate of healing is infection; this always retards healing. Other factors that may retard healing are dietary deficiencies, especially inadequate amounts of protein.⁷⁴ Lack of vitamin C prevents restoration of tensile strength, since this substance is essential in regeneration of collagen.⁴⁷ Lack of vitamin D interferes with healing of bones, as newly formed osteoid tissue is excessive, and fails to become calcified.

Restoration of tensile strength, as new fibrous tissue is formed during healing of wounds, was studied by incising the stomach in rats and allowing repair to proceed for varying lengths of time.³⁹ The animal was then killed, and the air pressure necessary to tear the wound open was determined. In this way, the rate with which tensile strength was restored was measured. The curve of recovery resembled the curve of wound closure as described above. After a lag period of about four days, recovery of tensile strength was most rapid at the beginning of repair, and became progressively slower, until tensile strength was fully restored after ten to fourteen days.

The Stimulus for Repair.—The nature of the stimulus that brings about repair or, more specifically, that excites cell migration and cell division, has long been the subject of lively

interest. Conceivably the stimulus might be (1) mechanical, e.g., release of tissue tension (Ribbert) when cells are destroyed, or (2) chemical—a chemical growth stimulus might be added or a growth-inhibiting substance might be removed; or the stimulus to repair might be some combination of these factors.

Although the nature of the stimulus is not definitely known, the evidence at present favors Carrel's explanation, that repair is stimulated by proteins or their derivatives that are released from injured cells. These substances are thought to supply living cells with material necessary for their growth.⁴ According to experiments of Hammett and Reimann,^{37, 84} growth-promoting substances must include the sulphydryl group which, they concluded, is essential for mitosis.

Among recent experiments supporting the view that products of injury are important in repair are those of Nettleship.⁷⁶ A portion of skin was removed from the rabbit's ear, and the average time for closure of the wound was determined (twelve to fourteen days). This time was reduced to ten to twelve days if a needle was inserted into the intact skin at the margin of the wound, thus causing slight injury. If, however, an extract of skin, i.e., products of injury from the skin, was injected through the needle into the margin of the wound, the time of healing was further reduced to seven or eight days. Extracts of other organs did not have this effect. In these experiments repair was brought about only by cell migration and multiplication, since the skin of the ear is too tightly attached to cartilage to allow appreciable contraction of the wound.

METAPLASIA

Metaplasia is a form of abnormal regeneration in which is produced a type of cell different from that normally found in a given location; e.g., squamous epithelium may replace columnar epithelium, bone may replace fibrous connective tissue (see also page 448).

During the development of the individual, cells progressively lose their power to form cells of different kinds. Thus the fertilized ovum is totipotential; it has the ability to differentiate into cells of all types. Cells of the embryonal layers are multipotential; they retain the power of forming cells of several types. However, in the adult stage, cells become unipotential, are able to form cells of a single type only, such as glandular epithelium or stratified squamous epithelium or bone.

Under certain conditions, cells regain the embryonal property of being able to form cells of different kinds, and the result is metaplasia. However, this recovered embryonal property is greatly



Fig. 56.—Metaplasia of epithelial lining of salivary duct. Replacement of columnar epithelium (shown on left) by stratified squamous epithelium (on right). ($\times 50$.)

limited; it affects only epithelial and connective tissue cells, and, though epithelial cells may form other types of epithelium, they cannot form any of the connective tissues, nor can the connective tissues form epithelium.

Metaplasia occurs under three conditions: chronic inflammation, vitamin A deficiency, and neoplasia. Thus, in chronic bronchitis, the columnar epithelium of the bronchus may be replaced by stratified squamous epithelium, and this change is seen especially in the lining of bronchiectatic cavities. Similar changes occur in the gall bladder when chronically irritated by stones. In prolapse of the uterus, the organ may hang from the vulva and more or less be turned inside out; the resulting exposure may induce metaplasia of the glandular lining cells into the squamous type. The same kind of epithelial change is found in the kidney pelvis as the result of chronic pyelonephritis.

In vitamin A deficiency, studied especially by Wolbach and Howe,¹⁰⁴ there is extensive metaplasia of the epithelium of the respiratory tract, eyes, salivary glands, and other organs. Here again, stratified squamous epithelium replaces the columnar and cuboidal varieties.

Connective tissue metaplasia occurs chiefly in chronic inflammations, and the best-known instance is the development of bone spicules where no bone has been before. Bone metaplasia may be found in the lung and in wounds in which there have been necrosis and calcification. Connective tissue cells assume the character of osteoblasts, laying down bony trabeculae which are provided with bone marrow.

Little is known about the cause of metaplasia. The best-established relation is with vitamin A deficiency, which so regularly causes metaplasia that one wonders whether all instances of epithelial metaplasia may be due to lack of, or inability to utilize, vitamin A.

The work of Wolbach and Howe clearly established that metaplasia occurs not through transformation of an adult cell of one type into one of another type, but rather through multiplication of cells, the resulting new ones assuming a different appearance from that of the parent cells. Usually the tendency in metaplasia is to replace cells of greater differentiation by those of less differentiated type, as, in instances given above, replacement of glandular epithelium by squamous cells, which are regarded as less differentiated in form and also in function; that is, they have lost secretory function. It is not understood what the mechanism of connective tissue metaplasia is, as seen in occurrence of cartilage or bone in new localities. As an explanation it has been suggested that in chronic inflammation there may be some fault in the chemical organizers, which determine in which direction and how far differentiation shall go; but whether the important principle of organizers is applicable to metaplasia is not known.

False metaplasia means that cells have been altered in form by forces applied to them from without. Thus the lining cells of cysts, originally columnar or cuboidal, may become flattened by increasing pressure of the cyst contents. False metaplasia is often seen in tumors, in which, as the result of pressure resulting from excessive cell multiplication, epithelial cells may be so compressed as to resemble cells derived from connective tissue, or, on the other hand, the cells on

free margins of connective tissue tumors may bulge and round up so that they somewhat resemble epithelium.

DURATION OF INFLAMMATION

Inflammation is said to be acute, subacute, or chronic, depending on its duration, which in turn depends on how long the injurious agent persists and continues to act. *Acute inflammation* lasts for a few days or two or three weeks; and thus its duration is brief and definite. In contrast, *chronic inflammation* lasts for months or years; its duration is indefinite. Subacute inflammation has intermediate duration, for weeks or months. Literally, the word acute means sharp or pointed, and originally referred to the sharpness with which a disease mounted to its height and then declined. Also, the word acute implied that the disease was relatively severe, but this idea of severity is not essential: we may speak of even such a mild lesion as herpes simplex (cold sore) as being acute, because of its brief and definite duration.

Subacute Inflammation

If an inflammatory process persists for longer than two or three weeks, it takes on histologic characters that are recognized as subacute; that is, neutrophiles are replaced by eosinophiles and lymphocytes, exudation is less prominent, while proliferative changes become more conspicuous, especially proliferation of the blood vessels and connective tissues. However, dense fibrous tissue, characteristically abundant in chronic inflammation, is not yet present in the subacute stage. Such changes as have just been described are commonly seen during healing of inflamed appendices and fallopian tubes.

As an example of subacute inflammation may be mentioned the cardiac lesion found in subacute bacterial endocarditis. This disease, usually caused by *Streptococcus viridans*, often lasts for six weeks or several months, and is characterized by destructive changes of the heart valves (especially the mitral and aortic) and by the presence on those valves of vegetations, that is, soft masses of thrombotic and other material attached to the leaflets. The subacute character of the

process is seen in the absence of granulocytes from the vegetations, which consist largely of platelets. Also, in the underlying valves, lymphocytes are numerous, though some granulocytes persist, and large polygonal fibrocytes are conspicuous. But the most prominent change is the great increase in blood capillaries, many of which are distended into cavernous channels.

Another instance of subacute inflammation is the subacute stage of glomerular nephritis. On microscopic examination, the glomeruli differ from those found in the acute stage of this disease chiefly in the greater frequency of epithelial proliferation known as the crescent or demilune. There is a notable change in the tubules, not seen in the earlier stage; they are somewhat atrophied and separated by newly formed connective tissue; this is the characteristic change in the subacute stage. On the other hand, densely fibrous glomeruli, typical of chronic glomerular nephritis, are absent.

Chronic Inflammation

Inflammation is said to be chronic when it lasts for a number of months or years, and has a duration that is indefinite. It is thus prolonged because the injurious agent persists in the tissues and continues to damage them, whether the cause of injury is a living organism or an irritating inanimate foreign body. Histologically, chronic inflammation differs from acute in a greater amount of proliferation of cells and connective tissues, while exudation is less conspicuous, being represented by lymphocytes and plasma cells rather than by polymorphonuclear leukocytes. As to necrosis, this plays an important part. Usually there are repeated episodes of necrosis, in response to which granulation tissue forms and becomes converted into fibrous tissue. Thus, in the course of time there is built up an increasing amount of scar tissue, which is the most characteristic feature of chronic inflammation.

In portal cirrhosis, these changes occur in all parts of the liver and cause profound alteration in histological appearance. Traversing the liver tissue are found interlacing bundles of scar tissue, infiltrated by lymphocytes and by groups of epithelial cells that probably represent

regenerated bile ducts. Instead of involving an entire organ, as does hepatic cirrhosis, a chronic inflammatory lesion may be confined to one region, as in peptic ulcer. In this lesion we find beneath granulations a triangular scar with base toward the defect in the mucous membrane, and apex toward the serous coat. The scar is in this instance advantageous, as it tends to prevent perforation.

and connective tissue. Eventually there is scarring. In the course of years, with extension of the infection throughout a lung, or kidney, almost the whole organ may be converted into fibrous tissue interrupted by cavities.

In some other infections, as in syphilitic chancre, the granuloma is chiefly composed not of epithelioid cells but of granulation tissue infiltrated with lymphocytes

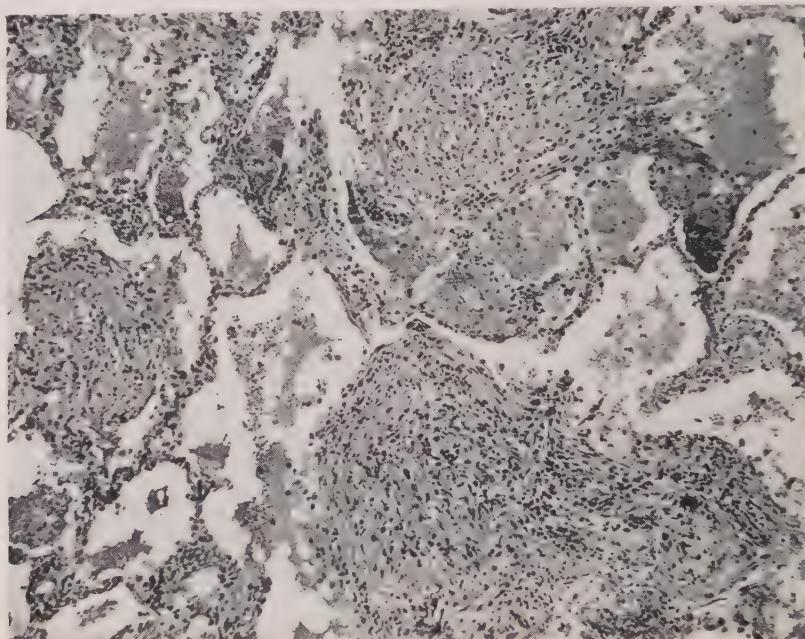


Fig. 57.—Chronic inflammation: organizing pneumonia. Because of delay in solution of fibrin, this substance acts as a foreign body, exciting chronic inflammation with fibrosis and cellular infiltration. ($\times 90$.)

Infectious Granulomas.—In chronic infections caused by microorganisms, the typical response is a granuloma. This is a firm nodule of newly formed tissue that varies in size from about 0.5 to 2 mm., or it may become much larger when neighboring lesions coalesce. These nodules are found in tuberculosis, syphilis, actinomycosis, leprosy, coccidioidomycosis, lymphogranuloma venereum, and other infections. Taking tuberculosis as an example, the tubercle consists essentially of macrophages which enlarge to form epithelioid cells (Figs. 30 and 31); some of these may coalesce to form Langhans giant cells. Often several tubercles fuse, and the center of the lesion becomes necrotic, the surrounding structures being stimulated to form new blood vessels

and plasma cells. In "eosinophilic granuloma" the cells are mostly eosinophiles.

Foreign Body Granuloma.—Following inhalation of silica dust, practically the same tissue changes may occur as in tuberculosis. Thus epithelioid and Langhans giant cells appear, and there are repeated episodes of necrosis and fibrosis. In the silicotic nodule, fibrous tissue is particularly dense and often appears laminated. Silicosis is an example of a granuloma caused by an inanimate foreign body, but other foreign bodies excite granulomas too. About insoluble sutures, splinters, or small projectiles, granulomas may form, in which giant cells of the foreign body type are the most conspicuous element. In these cells, nuclei are very numerous and are scattered

through the cytoplasm. These giant cells apply themselves closely to the suture or other object, but are unable to phagocytize it because of its large size. The end stage of this process is encapsulation with fibrous tissue. Oils, especially petrolatum, aspirated into the lung, or fatty substances such as cholesterol or fatty acids liberated in the tissues are potent stimuli for granuloma formation.

these may so narrow the urethra that passage of urine is prevented, the condition being known as stricture. Another venereal disease often responsible for stricture of the rectum is lymphogranuloma venereum; granulomatous tissue is formed and more and more fibrous tissue reaction follows, until the contracted scar tissue nearly or quite occludes the rectum.

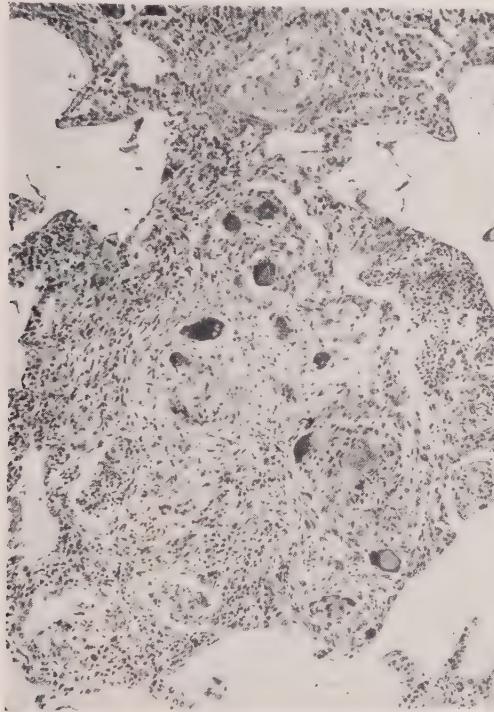


Fig. 58.

Fig. 58.—Granuloma produced by *Coccidioides immitis* in lung. The lesion consists of granulation tissue heavily infiltrated with several kinds of inflammatory cells of which giant cells are the most conspicuous. ($\times 100$.)

Fig. 59.—Granuloma produced by silica in the lung. The lesion consists mostly of fibrous tissue, in which carbon particles are conspicuous. Silica is associated with carbon in anthracite coal. ($\times 90$.)

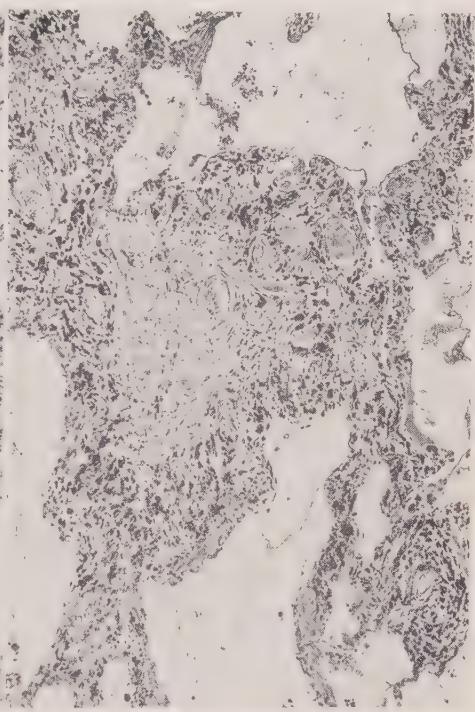


Fig. 59.

Effects of Chronic Inflammation.—Scarring may have many important consequences, chief among which is *obstruction*. Regional ileitis is an example of this, a chronic granulomatous condition of the intestine in which, over a period of months or years, scar tissue is built up, and, contracting, narrows and eventually obstructs the bowel. Thus it may necessitate surgical resection. Analogous effects are common in the urethra of the male in chronic gonorrhea. Fibrous adhesions form on the mucosa, and contraction of

A different effect of chronic inflammation sometimes occurs in pericarditis if the inflammatory process continues a long time, as it may in tuberculosis. As the result of continued shrinking of dense connective tissue, pressure is made on the heart, which becomes unable to expand adequately in diastole. The result is decreased cardiac output, increased venous pressure, and a chain of related events that impairs cardiac function.

From these considerations, it is evident that damage in chronic inflammatory

processes results chiefly from repeated episodes of necrosis. Such necrosis, especially when it involves many groups of cells, stimulates repeated formation of granulation tissue, and consequently leads to scarring and thus ultimately to a whole series of functional changes tending to cripple the organ or even to threaten life.

Since inflammation means reaction of tissue to injury, the term inflammation should not be applied to scarred areas in which all reactive processes have ceased. Thus we frequently encounter pleural, pericardial, or peritoneal adhesions as residua of inflammations that ran their course perhaps decades ago. Under these conditions it is better to speak of fibrosis, or to specify pleural adhesions, myocardial scars, etc., than to use such terms as chronic pleurisy and chronic myocarditis.

The gross appearance of an organ, the site of chronic inflammation, may be inferred from what has preceded. Taking the cirrhotic liver as an example, the organ tends to become small as fibrous tissue shrinks; the color is less red as vascularity decreases. The shape is distorted by scarring, the hobnailed liver of cirrhosis being a notable example of this. The consistency is considerably increased, because of the hardness of fibrous tissue. The cirrhotic liver may become so tough that it cannot be torn by hand.

Similar changes occur in other organs. Recall the dense scars often found in tuberculous or silicotic lungs, the small, granular, pale, and hard kidneys of chronic glomerular nephritis. However, a chronically inflamed organ is not necessarily small; for example, the leg or serotum in elephantiasis is enormously increased in size from obstruction of lymphatics.

The cardinal signs of inflammation tend to disappear as the condition becomes chronic. Vascular dilatation is often brief; the red color gives way to purple, which fades as the blood supply diminishes. Excessive heat disappears together with redness. Swelling decreases with decrease in the exudate. Pain is generally less severe or may disappear.

The term **recurrent inflammation** is used when the exciting cause acts not continuously, as in chronic inflammation,

but intermittently. A good example is appendicitis, a condition in which there are commonly repeated episodes of acute inflammation, separated by periods of weeks or months during which the patient is free from symptoms and repair occurs at the site of injury. Each period of repair adds some scar tissue, until the appendix may become almost entirely fibrous and no longer possesses a lumen.

Histologically, the appearance is mixed: recent inflammation is indicated by neutrophiles or eosinophiles, but in addition there are residua of former inflammation, that is, lymphocytes and fibrous tissue.

References

- Abramson, H. A.: J. Exper. Med. **46**: 987, 1927, and J. Gen. Physiol. **11**: 743, 1928 (leukocyte emigration).
- Addis, T., and Lew, W.: J. Exper. Med. **71**: 325, 1940 (restoration of lost organ tissue).
- Altschuler, C. H., and Angevine, D. M. Am. J. Path. **27**: 141, 1951 (mucopolysaccharides and serous inflammation).
- Arey, L. B.: Physiol. Rev. **16**: 327, 1936 (wound healing).
- Barnes, J. M.: Brit. J. Exper. Path. **21**: 264, 1940 (enzymes of lymphocytes and polymorphonuclear leukocytes).
- Berry, J., and Spies, T. D.: Medicine **28**: 239, 1949 (phagocytosis).
- Blumenfeld, C. W.: Arch. Path. **36**: 493, 1943 (mitotic activity in regenerating epidermis).
- Byars, L. I., and Letterman, G. S.: Surg., Gynec. & Obst. **89**: 583, 1949 (homografts of skin).
- Cameron, G. R.: J. Path. & Bact. **35**: 933, 1932 (inflammation in earthworms).
- Cameron, G. R.: J. Path. & Bact. **38**: 44, 1934 (inflammation in insects).
- Campbell, D. H.: J. Infect. Dis. **71**: 270, 1942 (experimental eosinophilia).
- Carrel, A., and Hartmann, A.: J. Exper. Med. **24**: 429, 1916 (relation between size of a wound and rate of its cicatrization).
- Clark, E. K., and Clark, E. L.: Anat. Rec. **24**: 137, 1922 (reaction of living cells).
- Clark, E. R., and Clark, E. L.: Am. J. Anat. **46**: 149, 1930 (relation of monocytes of blood to tissue macrophages).
- Clark, E. R., and Clark, E. L.: Am. J. Anat. **57**: 385, 1935 (changes in blood vascular endothelium).
- Clark, E. R., Clark, E. L., and Rex, R. O.: Am. J. Anat. **59**: 123, 1936 (polymorphonuclear leukocytes).
- Cohn, R.: Anat. Rec. **75**: 195, 1939 (postnatal growth of lung).
- Cohnheim, J.: Arch. f. path. Anat. u. Physiol. **40**: 1, 1867.
- Cannon, W. B.: The Wisdom of the Body, New York, 1932, W. W. Norton & Co., Inc.
- Conway, J. H.: Proc. Soc. Exper. Biol. & Med. **34**: 353, 1936 (subcutaneous temperatures in localized infections).
- Cottingham, E., and Mills, C. H.: J. Immunol. **47**: 493, 1943 (phagocytosis in vitamin deficiency).
- Dougherty, T. F., and White, A.: Am. J. Anat. **77**: 81, 1945 (alterations in lymphoid tissue induced by adrenal cortical secretion).
- DuNouy, P. L.: J. Exper. Med. **24**: 461, 1916 (cicatrization).
- Ebbecke, U.: Arch. f. d. ges. Physiol. **169**: 1, 1917 (vasomotor reactions of the skin).
- Ehrlich, W. E., Drabkin, D. L., and Forman, C.: J. Exper. Med. **90**: 157, 1949 (plasma cells as source of antibodies).
- Ehrlich, W. E., Harris, T. N., and Mertens, E.: J. Exper. Med. **83**: 373, 1946 (failure of macrophages to form antibodies).

27. Ehrlich, W. E., Seifert, J., Auburn, H. E., and Begany, A. J.: Proc. Soc. Exper. Biol. & Med. **70**: 183, 1949 (mast cells as a source of heparin).
28. Fenn, W. O.: J. Gen. Physiol. **3**: 439, 1921 (phagocytosis).
29. Fenn, W. O.: J. Gen. Physiol. **4**: 373, 1922 (response of living cells to contact with solid bodies).
30. Field, M. E., Drinker, C. K., and White, J. C.: J. Exper. Med. **56**: 363, 1932 (lymph pressures in sterile inflammation).
31. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Am. J. M. Sc. **183**: 104, 1932 (myeloid cell hyperplasia of bone marrow).
32. Garber, C. F., and Bush, L. F.: in Monographs on Surgery, New York, 1950, Thomas Nelson & Sons, p. 333.
33. Gay, F. P., Clark, A. R., and Linton, R. W.: Arch. Path. **1**: 857, 1926 (histologic basis for resistance to streptococcus).
34. Glenn, W. W. L., Gilbert, H. H., and Drinker, C. K.: J. Clin. Investigation **22**: 609, 1943 (burns).
35. Glenn, W. W. L., Peterson, D. K., and Drinker, C. K.: Surgery **12**: 865, 1942 (flow of lymph from burned tissue).
36. Greene, H. S. N.: Cancer Research **3**: 809, 1943 (heterologous transplantation).
37. Hammett, F. S., and Reimann, S. P.: J. Exper. Med. **50**: 445, 1929 (cell proliferation response to sulphydryl).
38. Harris, T. N., Grimm, E., Mertens, E., and Ehrlich, W. E.: J. Exper. Med. **81**: 73, 1945 (lymphocyte in antibody formation).
39. Harvey, S. C.: Arch. Surg. **18**: 1227, 1929 (velocity of growth of fibroblasts in the healing wound).
40. Heilbrunn, L. V.: An Outline of General Physiology ed. 3, Philadelphia, 1952, W. B. Saunders Co., p. 652.
41. Huff, C. G.: Physiol. Rev. **20**: 68, 1940 (immunity in invertebrates).
42. Husfeldt, E.: Ztschr. f. physiol. Chem. **194**: 137, 1931 (proteolytic enzyme in leukocytes).
43. Hyman, L. H.: Biol. Symposia **2**: 241, 1941 (regeneration).
44. Ingle, D. J.: J. Clin. Endocrinol. **10**: 1312, 1950 (review of biologic properties of cortisone).
45. Jacoby, F.: J. Physiol. **91**: 22, 1937-38 (chemotaxis in macrophages).
46. Jaffe, R. H.: Physiol. Rev. **11**: 277, 1931 (reticulo-endothelial system in immunity).
47. Jones, C. M., Bartlett, M. K., Ryan, A. E., and Drummond, G. D.: New England J. Med. **229**: 642, 1943 (healing of wounds and vitamin C).
48. Kettle, E. H.: J. Path. & Bact. **35**: 395, 1932 (interstitial reactions caused by dusts).
49. Landis, E. M.: Physiol. Rev. **14**: 404, 1934 (capillary permeability).
50. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, 1927, Shaw & Sons, Ltd.
51. Lewis, T.: Pain, New York, 1942, The Macmillan Co., p. 113.
52. Lewis, W. H.: The Harvey Lectures **21**: 77, 1927 (transformation of mononuclear blood cells into macrophages).
53. Lewis, W. H.: Bull. Johns Hopkins Hosp. **49**: 17, 1931 (pinocytosis).
- 53a. Lewis, W. H.: Am. J. Cancer **29**: 666, 1937 (pinocytosis by malignant cells.)
54. Lewis, W. H.: Bull. Johns Hopkins Hosp. **55**: 273, 1934 (locomotion of lymphocytes).
55. Lewis, W. H.: Arch. f. exper. Zellforsch. **23**: 1, 1939 (mechanisms of locomotion).
56. Loeb, L.: The Biological Basis of Individuality, Springfield and Baltimore, 1945, Charles C Thomas Co., p. 62.
57. Idem: p. 6 ff.
58. Longmire, W. P., Jr., and Smith, S. W.: Arch. Surg. **62**: 443, 1951 (homologous transplantation).
59. Lucké, B.: Am. J. Path. **20**: 595, 1944 (epidemic hepatitis).
60. Lucké, B., and McCutcheon, M.: Arch. Path. **10**: 662, 1930 (effect of injury on cellular permeability).
61. Lucké, B., Strumia, M., Mudd, S., McCutcheon, M., and Mudd, E. B. H.: J. Immunol. **24**: 455, 1933 (comparative phagocytic activity of macrophages and polymorphonuclear leukocytes).
62. McCutcheon, M.: Physiol. Rev. **26**: 319, 1946 (chemotaxis in leukocytes).
63. Mast, S. O.: Physiol. Zool. **5**: 1, 1932 (response in amoeba).
64. Maumenee, A. E., and Kornblueth, W.: Am. J. Ophth. **31**: 1384, 1948 (survival of corneal transplants).
65. Menkin, V.: J. Exper. Med. **67**: 145, 1938 (mechanism of cell migration).
66. Menkin, V.: Arch. Path. **30**: 363, 1940 (leukocytosis promoting factor).
67. Menkin, V.: Dynamics of Inflammation, New York, 1940. The Macmillan Co., p. 202.
68. Metchnikoff, E.: Lectures on the Comparative Pathology of Inflammation, English transl. by F. A. and E. H. Starling, London, 1893.
69. Meyer, K., and Rapport, M. M.: Science **113**: 596, 1951 (mucopolysaccharides of ground substance of connective tissue).
70. Michels, N. A.: Arch. Path. **11**: 775, 1931 (plasma cell).
71. Miller, F. R.: J. Exper. Med. **54**: 333, 1931 (histogenesis of plasma cells).
72. Mills, C. A., and Cottingham, E.: J. Immunol. **47**: 503, 1943 (phagocytosis in protein deficiency).
73. Moore, F. D., and Tobin, L. H.: J. Clin. Investigation **21**: 471, 1942 (localization in inflammatory lesions).
74. Morris, H. P., Duknik, C. S., and Dunn, T. B.: J. Nat. Cancer Inst. **5**: 283, 1945 (epithelialization of paired skin wounds).
75. Mudd, S., McCutcheon, M., and Lucké, B.: Physiol. Rev. **14**: 210, 1934 (phagocytosis).
76. Nettleship, A.: Am. J. Clin. Path. **13**: 349, 1943 (rate of epithelialization).
77. Opie, E. L.: Physiol. Rev. **2**: 552, 1922 (intracellular digestion).
78. Opie, E. L.: J. Exper. Med. **39**: 659, 1924 (fate of antigen [protein] in an animal immunized against it).
79. Opie, E. L.: J. Immunol. **9**: 259, 1924 (Arthus phenomenon).
80. Padgett, E. C.: Skin Grafting, Springfield and Baltimore, 1942, Charles C Thomas.
81. Ponder, E., and Macleod, J.: J. Exper. Med. **67**: 839, 1938 (white cell morphology).
82. Popper, H. P.: Am. J. Path. **15**: 651, 1939 (serous inflammation).
83. Porter, K. R., and Vanamee, P.: Proc. Soc. Exper. Biol. & Med. **71**: 513, 1949 (formation of connective tissue fibers).
84. Reimann, S. P.: J. A. M. A. **94**: 1369, 1930 (thiocresol to stimulate wound healing).
85. Rich, A. R.: Physiol. Rev. **5**: 182, 1925 (formation of bile pigment).
86. Rich, A. R.: Physiol. Rev. **21**: 70, 1941 (hypersensitivity in infections).
87. Rich, A. R.: The Pathogenesis of Tuberculosis, ed. 2, Springfield and Baltimore, 1951, Charles C Thomas, p. 603.
88. Idem: p. 600.
89. Rich, A. R., and Gregory, J. E.: Bull. Johns Hopkins Hosp. **73**: 239, 1943 (lesions from anaphylactic hypersensitivity).
90. Rich, A. R., and McKee, C. M.: Bull. Johns Hopkins Hosp. **64**: 434, 1939 (pathogenicity of avirulent pneumococci for animals deprived of leukocytes).
91. Rivers, T. M.: Am. J. Path. **4**: 91, 1928 (filterable viruses).
92. Robertson, O. H.: Physiol. Rev. **21**: 112, 1941 (phagocytosis of foreign material in lung).
- 92a. Rössle, R.: Arch. f. path. Anat. **311**: 252, 1943 (Ueber die serösen Entzündungen der Organe).
93. Rosenthal, S. K., and Minard, D.: J. Exper. Med. **70**: 415, 1939 (histamine as chemical mediator for cutaneous pain).
94. Rous, P., and McMaster, P. D.: J. Exper. Med. **39**: 425, 1924 (liver requirement of fasting organism).
95. Spector, W. G.: J. Path. & Bact. **68**: 93, 1951 (role of some higher peptides in inflammation).
96. Stearns, M. L.: Am. J. Anat. **66**: 133, 1940 (development of connective tissue).

97. Strumia, M. M., and Boerner, F.: Am. J. Path. **13**: 335, 1937 (phagocytic activity of circulating cells in leukemia). For opposing view, see Hertzog, A. J.: Am. J. Path. **14**: 595, 1938 (phagocytic activity of human leukocytes with reference to their type and maturity).
98. Sturgis, C. C., and Bethell, F. H.: Physiol. Rev. **23**: 279, 1943 (variations in normal leukocytes).
99. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: J. A. M. A. **137**: 1005, 1948 (eosinopenic response to ACTH).
100. Toolan, H. W., and Kidd, J. F.: Fed. Proc. **8**: 373, 1949 (necrobiosis of cancer cells following adhesion by lymphocytes).
101. Weeks, R. E., and Gunnar, R. M.: Arch. Path. **48**: 178, 1949 (role of histamine in inflammation).
102. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, 1925, W. B. Saunders Company, p. 288.
103. Werthemann, A.: Arch. f. path. Anat. **270**: 605, 1928-29.
104. Wolbach, S. B., and Howe, P. R.: J. Exper. Med. **42**: 753, 1925 (tissue changes following deprivation of fat-soluble A vitamin).
105. Wood, W. B., Jr.: Ann. Int. Med. **27**: 347, 1947 (surface phagocytosis).
106. Wood, W. B., Jr., and Smith, M. R.: J. Exper. Med. **90**: 85, 1949 (surface phagocytosis).
107. Yoffey, J. M.: Biol. Rev. **25**: 314, 1950 (mammalian lymphocytes).

Chapter 4

DEGENERATIVE CHANGES AND DISTURBANCES OF METABOLISM

W. A. D. ANDERSON

ATROPHY

Atrophy is an acquired decrease in size of a portion of the body, of an organ, of tissues, or of individual cells. The term implies that full size once was present, and hence is to be distinguished from hypoplasia, aplasia, and agenesia. Hypoplasia refers to a lack of development to a full or mature size, aplasia to an almost complete lack of development, proper form and structure failing to be acquired, and in agenesia even the anlage of the part was lacking or faulty, so that the part is completely absent. Atrophy also is to be distinguished from reduction in size of an organ or part by acute destruction or necrosis, as by bacterial or other types of injury.

Reduction in size of an organ may be due either to decrease in the number of its structural units, or to the decrease in size of the individual units, or to both. In most cases in which a marked degree of atrophy of an organ has occurred, there is a reduction in the number of functional units or cells composing the organ. Often the decrease of size of an organ does not match the numerical reduction of its component functional units, as the lost functional tissue may be partly replaced by fibrous or fatty tissue.

Not all atrophy is pathologic, but certain organs and tissues normally undergo reduction in size or disappearance at certain periods of life, their persistence constituting an abnormal condition. During embryonic or fetal life, certain structures, such as the thyroglossal duct, normally undergo atrophy. During infancy there occurs a physiologic atrophy of the thymus, and of the inner zone of the adrenal cortex. Lymphoid tissues tend to atrophy as an individual progresses to maturity. Following parturition the hypertrophied uterus normally decreases to original size, the muscle fibers shrinking in average length from about 208 microns to 24 microns. The ovaries and breasts atrophy at the

menopause. With the aging process many tissues undergo atrophic changes.

Atrophy may be unaccompanied by other degenerative changes, but very often the elements undergoing atrophy show pigmentation, or fatty and other types of degeneration. In atrophic organs, the less specialized connective tissues are less affected than functional parenchymal elements, and hence often appear relatively increased. There is often an actual increase or replacement by fibrous or fatty tissue in organs in which functional units have decreased in number. Fat tissue replacement is common in atrophy of pancreatic and of renal tissue. Increased pigment content is common in atrophic cells, and probably is one example of the accumulation in the atrophic cell of a metabolic product of which the normal cell more readily rids itself. Pigmentation is particularly prominent in atrophied cardiac muscle, wherein brownish-yellow granules appear prominently at the poles of the nuclei.

Atrophy is brought about by some change or disturbance of the metabolism of the involved cells. Such metabolic change appears most often to be due to interference with the nutrition of the cells, either from absence of essential nutritive substance, interference with the cellular absorption of nutritive material, or prevention of nourishment reaching the cells as a result of disturbance of vascular supply. The actual chemical mechanism which is suggested to be acting in cellular atrophy is an increased activity of intracellular proteolytic enzymes (cathepsin) as a result of acid accumulation and increased hydrogen-ion concentration resulting from decreased oxidative metabolism.¹

Types of Atrophy

Although almost all atrophies in the final analysis are due to changes in the nutrition and metabolism of the involved cells, they are commonly classified as general or local, according to the cause or mechanism of the disturbance of cellular nutrition and metabolism.

General atrophy, involving widespread and numerous tissues of the body, occurs in starvation or inanition, and in the process of aging (senile atrophy).

Atrophy of starvation may be due to

lesions of the digestive tract preventing the taking or assimilation of food, such as stricture of the esophagus, or to loss of appetite or ability to relish food without organic cause (*anorexia nervosa*) as well as to lack of essential foodstuffs. Profound degrees of wasting and emaciation of the body may result. The gastrointestinal tract itself participates in the atrophy as a result of cessation of its normal functional activities. The central nervous system, bones, and muscles in active use participate less in the atrophy than other tissues of the body. In some cases of prolonged chronic infections and advanced cancerous states, similar degrees of generalized wasting may be found. While often attributed to absorption of toxins or metabolic poisons, the wasting appears in most cases to be explainable on the basis of nutritive disturbance.

Senile atrophy, present in variable degree in many organs and tissues in advanced age, appears to have several causative factors acting on the various tissues. The process of aging in various organs and tissues has been a subject of much interest and study in recent years.² In a sense the physiologic atrophy of the thymus and of the ovaries and uterus at the menopause represent aging in these tissues. The causes of the atrophic changes in various tissue with aging vary. Some, such as atrophy of the breasts, are due to changes in endocrine influence. Others, such as atrophy of lymphoid tissue, appear to be an involutionary change due to decrease of growth stimuli. Elastic tissues, as in the skin and blood vessel walls, appear to undergo irreversible chemical changes with aging. Many of the atrophies of aging appear to be due to local decrease of vascular supply, the result of sclerosis of arteries with narrowing of their lumens. Even the bones and the nervous system participate prominently in the atrophy of aging. The long bones and the bones of the face and skull undergo lacunar resorption, become lighter, more porous, and fragile. The brittleness and fragility as a result of these senile changes cause them to fracture with relatively slight trauma. The upper end of the femur is so affected with particular frequency. The brain involved by senile atrophy appears shrunken, has

widened sulci, slight enlargement of the ventricular system, and loss of ganglion cells with gliosis. Mental changes of mild to marked degree (*senile dementia*) accompany the senile atrophy of the nervous system. Cerebral arteriosclerosis is usually marked in such cases.

Local atrophy may be due to disuse of a part or loss of motor nerve supply, to pressure, to change or loss of endocrine stimulation, and perhaps in certain circumstances to overwork or to toxic injuries.

Disuse atrophy, the result of inactivity of an organ or tissue is of common occurrence. Forced inactivity of muscles soon results in decrease in size, the atrophy being particularly marked when there is muscular paralysis due to loss of motor nerve supply (*neurotrophic atrophy*) such as commonly results from anterior poliomyelitis. Bones also soon show atrophy, become more porous, and show decreased calcium content when forced inactivity prevents their regular functional activity of weight-bearing. Glandular organs forced to inactivity by occlusion of their ducts soon show atrophy of their functional cells. In the case of the pancreas, occlusion of the duct results in atrophy of the acinar tissue, while the endocrine islet tissue, the secretion of which goes directly into the blood stream, remains relatively unaffected.

Pressure atrophy is commonly the result of prolonged or continuous pressure upon a local area or group of cells. Pressure apparently affects cells by interference with their vascular and lymphatic supply, thus preventing proper nutrient reaching and being absorbed by the cells. Pressure exerted by a growing tumor causes such atrophy of the adjacent nontumor tissue. Amyloid, deposited within tissue spaces, brings about atrophy of the adjacent cells. The constant pulsating pressure of an aneurysm causes erosion and atrophy of any tissue, even bone, on which it impinges. Obstruction of a ureter with distention of the pelvis of the kidney (*hydronephrosis*) eventually leads to marked atrophy of renal tissue.

Endocrine atrophy occurs in organs which depend for their functional activity on endocrine stimulation, when such stimulation is decreased or ceases. Cessa-

tion of pituitary activity results in atrophic changes in the thyroid, adrenals, ovaries, and other organs which are influenced by pituitary hormones (Simmond's disease).

Atrophy from overwork occurs rather infrequently. Increased functional demand ordinarily causes hypertrophy, but when forced excessive use is of prolonged duration it may eventually lead to atrophy. Such a result is sometimes seen in accessory muscles of respiration in severe pulmonary emphysema, and is said to occur also in certain localized muscle groups as a result of excessive occupational use.

Toxic atrophy, in which as a result of toxic influence cells of an organ undergo gradual atrophic changes apart from any acute degeneration or destructive action and apart from some nutritional disturbance, probably occurs rarely if at all. Certain cases of Addison's disease (see page 1034) have as their basis a bilateral atrophy of the adrenal cortices. While this has been postulated as due to some unknown toxic influence on the adrenal cortical tissue, it is not proved that it may not have its origin in some acute destructive or necrotizing injury of the adrenal cortices.

DISTURBANCES OF FAT METABOLISM AND ADIPOSE TISSUE

Fatty substances form a considerable proportion of all cells and tissues, and in addition are stored in large quantities in the cells of specialized connective tissues. This latter tissue, known as adipose tissue, constitutes about 18 per cent by weight of an individual of average nutrition. Disturbances in the amount, distribution, type, demonstrability, or stainability of various fatty substances in various functioning parenchymatous cells, as well as disturbances in adipose tissue, are very common in disease processes. Disturbances in metabolism of fatty substances form a prominent part of the pathologic picture in various organs and tissues in many diseases.

No attempt will be made here to review the normal chemistry and metabolism of fatty substances, details of which are available in textbooks of biochemistry and physiology. Neutral fats are triglyceride esters chiefly of the higher fatty acids, oleic, palmitic, and stearic. Lipoids

form a more indefinite group of substances, their main common characteristic being a solubility in fat solvents. Among important lipoids are cholesterol and its esters, which are anisotropic (doubly refractive), lecithin (phospholipid), and cerebrosides. The term lipid is used to include both the neutral fats and lipoids. Neutral fats and some lipoids may be hydrolyzed under pathologic conditions in tissues to form soaps. Calcium soaps thus formed are insoluble. Disturbances in absorption of dietary fatty substances may occur from gastrointestinal tract disturbances or inability to digest fat (steatorrhea), e.g., as a result of pancreatic disease (see page 850). Deficiency of fat-soluble vitamins may result in such cases, particularly of vitamin D, leading to osteomalacia,³ or of vitamin A.

Fatty substances in the tissues are normally held within the cytoplasm of cells, or transported in lymph or blood. Fatty substances normally are not found free in tissue spaces between cells and, when fat occurs free in tissue spaces under pathologic conditions, it elicits an inflammatory reaction, usually of foreign-body type. Under normal conditions, fat is histologically visible only in adipose tissue, in small amounts in the liver, an organ normally concerned in fat metabolism, in the cortex of the adrenal glands (lipoids), the corpus luteum, etc. Nevertheless, all organs contain a certain amount of essential, combined, or masked fat which can be extracted from the tissues by chemical methods. In the case of heart muscle this extractable fat forms about 2 per cent by weight of the tissue. In most tissues the amount of this intimately combined fat does not vary with the state of nutrition, but remains constant even in conditions of starvation and emaciation. In skeletal muscle, however, the fat content apparently may be increased by overnutrition.

Histologic demonstration of fat in tissues depends on its physical characteristics or on chemical union with certain substances. In the usual routine method of preparation of tissues for microscopic examination fat solvents are used which dissolve out the fat and leave clear areas at the site. Crystals of lipoids, such as cholesterol, dissolve out, leaving cleftlike spaces.

Lipoids in tissues may be investigated by a polarizing microscope. Compounds of lecithin and cholesterol are optically active, and rotate polarized light (doubly refractile, see Fig. 460, page 577). Investigation of lipid crystals also may be done by estimation of their melting point on a warm stage.

Osmic acid oxidizes unsaturated fats (such as olein) to form an insoluble black compound, the tissue then being given the usual paraffin

preparation. This will demonstrate black fatty substance in fatty degeneration of heart, kidney, and other organs. Osmic acid has had its greatest use, with the technique of Marchi or of Weigert, in the demonstration of abnormalities of the myelin of nerves (see page 1282).

Stains, such as Sudan III or scarlet red, which dissolve in and color neutral fats, are commonly used to stain fat in tissues. They are used with frozen sections.

Adipose Tissue

Adipose tissue is a specialized type of connective tissue which acts as a storage depot for ingested fat which is in excess of the immediate metabolic needs of the individual. It is found mainly in the subcutaneous tissue, omentum, mesentery, perirenal tissue, and bone marrow. Wells⁷ has reviewed the evidence that adipose tissue is a special type of tissue, and not just ordinary connective tissue which has accumulated a fat content. The embryonic origin of adipose tissue has close similarities to that of lymphoid tissue, which has made clearer the frequent tendency of fat to replace lymphoid tissue, and the close relationship of adipose tissue and bone marrow. Adipose tissue is not an inactive tissue, but there is evidence of a constant turnover of fat in the fat depots. Activities of adipose tissue other than storage of fat alone have been postulated, such as a role in water metabolism, and functions similar to those of the reticuloendothelial system.

Excess of adipose tissue is most often generalized (obesity) but may be localized as an excess limited to certain areas of the body, as tumors of fatty tissue (lipomas) and as replacement of atrophic parenchymatous tissue (e.g., renal lipomatosis).

Obesity.—Obesity is the condition in which there is an abnormally large amount of adipose tissue. Insurance statistics indicate that obesity, even of mild degree, is associated with significantly increased rates of mortality in middle and later ages. Hereditary and environmental factors have both been shown to have important roles in the development of obesity, but metabolic studies have indicated that obesity is invariably the result of an energy intake by the body greater than its total dissipation (positive energy balance). Endocrine factors appear to be more important in determining the distribution of the excessive adipose tissue than in causing a change in metabolic energy balance. The steroid hormones of the adrenal cortex or gonads appear to be active in influencing the distribution of body fat. Disturbance in water balance is common in obese individuals.

Adiposis dolorosa is a term proposed by Dercum for certain cases of generalized obesity in which pain and tenderness of the fat deposits is an outstanding feature. Adiposity may be more prominent in certain localized areas, with formation of tumorlike masses. Marked asthenia and mental abnormalities are usually present. Nonspecific changes in various endocrine organs have been described. The histologic appearance and the chemical composition of the fatty deposits

in Dercum's disease does not appear to be different from that in other cases of obesity. It occurs chiefly in women.

Localized Excessive Adipose Tissue.—Specialized or localized masses of fatty tissue are found in certain animals, as in the hump of the camel. Among examples of localized obesity in human beings is the condition of steatopygia, an excess fatty accumulation in the buttocks, and common as a racial characteristic among Bushmen and Hottentots. Excessive adipose tissue in the cervical region, or symmetrical fatty tumors of the neck, has often been referred to as "Madelung's neck" following description of such cases in the German literature by Madelung in 1888.

Lipodystrophy progressiva is characterized by loss of adipose tissue in certain regions of the body, while remaining parts retain their adipose tissue or may show increase in fat. Loss of fat, even to an emaciated degree, may occur in the upper half of the body, while the lower half of the body retains abundant adipose tissue. It occurs mainly in women, and mild degrees are probably quite common. Wells has reported a disappearance of the specialized fat-holding cells of adipose tissue in the emaciated areas.

Insulin lipodystrophy is a localized loss of fat in areas where insulin has been injected. The adipose tissue disappears in the local area without active inflammatory reaction. No satisfactory explanation has been found (see Fig. 763, page 867).

Inflammation of Adipose Tissue.—Injuries of adipose tissue with necrosis or rupture of the fat-holding cells is not uncommon, and gives rise to an inflammatory reaction. Fat necrosis is most often the result of pancreatic disease, with release and activation of fat-splitting enzymes (see page 852). Traumatic injury to subcutaneous or bone marrow fat also may cause inflammatory reaction. Release of lipid material into breast tissues also occurs quite commonly (see page 1106). The inflammatory reaction resulting from localized necrosis of adipose tissue (lipogranulomatosis) often simulates the histologic appearance of tuberculosis (see page 238).

Sclerema adiposum neonatorum is a more specific inflammatory disturbance of adipose tissue. In affected newborn infants the subcutaneous fat feels hard and rigid. The adipose tissue, both subcutaneous and internal, shows varying degrees of degeneration, necrosis, and crystallization, with a granulomatous chronic inflammatory reaction and scarring. Obstetric trauma has been thought to be the precipitating local injury in some cases. The adipose tissue is said to be deficient in olein content, and hence to have an abnormally high melting point.

Nonsuppurative nodular panniculitis (Weber-Christian's disease) is a condition of unknown etiology, characterized by recurrent fever and peculiar widespread nodular nonsuppurative inflammation and necrosis of subcutaneous and sometimes internal fatty tissue. Involved areas are tender. The lesions appear to begin as small areas of lipid-containing macrophages, progress through a stage of necrosis with lymphocytes, neutrophiles, and occasional giant

cells, and finally undergo fibrosis. In but few of the reported cases, death has been due to the disease.

Intestinal Lipodystrophy (Whipple's Disease).

—Intestinal lipodystrophy is a rare primary disturbance of intestinal absorption of fat. Deposits of fat and fatty acids occur in intestinal and mesenteric lymphatic tissues. Small firm elevated nodules occur in the intestinal mucosa and on peritoneal surfaces. They contain fatty material and show a granulomatous inflammatory reaction which proceeds to fibrosis. Abdominal viscera may become matted together. Lymphoid tissue and lymph nodes show dilated sinuses containing fatty debris. The disease progresses, with loss of weight and strength, microcytic anemia, and tender swelling of the abdomen with steatorrhea. The etiology is unknown but has been suggested to be a fault in bile salt metabolism.²²

Fatty Infiltration

Fatty infiltration is the condition of excessive accumulation of fat in connective tissue fibers between parenchymatous cells of organs. The parenchymatous structures, abnormally separated by the fatty accumulation, may be subject to some interference with their function, and tend to undergo atrophy. The condition is seen most markedly in the heart and pancreas, and often in individuals who show generalized obesity. In the case of the heart, the fatty tissue of the subepicardium extends irregularly into the myocardium, separating the myocardial fibers, the muscle fibers tending to undergo atrophy. In mild cases, the extension of the fatty tissue is not very far into the myocardium, but in severe cases there is deep extension. In fatty infiltration of the pancreas, the fat tissue which normally is found around the organ extends deeply and separates the lobules. In severe cases, the pancreas may appear to consist mainly of fatty tissue, composed of but a relatively small proportion of parenchymatous lobules.

Fatty Metamorphosis of the Liver.

—Fatty infiltration in the liver is a different condition, in that the term is used in reference to excessive accumulation of fat in the parenchymatous cells of the liver. The liver is an organ which plays an important role in the normal metabolism of lipids. Excess accumulation of fat occurs in liver cells very commonly in metabolic disturbances, and apparently apart from primary injury or degeneration of the liver cells. However, a true

fatty degeneration, in which fat appears in liver cells as a result of their injury, also occurs.

It was originally thought that fatty infiltration of the liver resulted from transport of fat to the liver from elsewhere in the body due to excess of food fat, whereas fatty degeneration was the result of an unmasking of fat or a change in chemical form of substances already present within the cell due to cellular injury. It was believed that morphologic distinction between these forms could be made, in the former case the fat appearing in the liver cells as large, and often single, vacuoles, and in the latter the fat droplets being tiny and numerous. It is now known that the premises and morphologic basis of this distinction are unreliable or fallacious, and the terms "fatty infiltration" and "fatty degeneration" are tending to be discarded in the case of the



Fig. 60.—Fatty infiltration of heart. Adipose tissue between myocardial fibers.



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and differential staining. Consequently, variations in the amount and distribution of glucose in tissues cannot be studied histologically.

Glycogen, however, can be demonstrated in tissues as it is not dissolved out during fixation of tissues in 95 per cent or absolute alcohol, or in Carnoy's fluid, and in tissues it may be stained a crimson color by Best's carmine stain. Variations from its normal amount and distribution in tissues are readily demonstrated and form important features of certain disease processes.

Glycogen is a condensation product of dextrose, and similar to starch in its structure and chemistry. It exists in cells in a colloidal state, certain proteins within the cell acting to protect it in this state. Synthesis of glycogen is an important function of the liver. As a storage form of carbohydrate in tissues, particularly the liver and voluntary muscle, glycogen is readily convertible into glucose, and is available to meet sudden demands for carbohydrate by the body. Glycogen is important also, however, in maintenance of functional health and well-being of cells. This seems to be particularly true of the liver, where a good store of glycogen protects the protein structure of the hepatic cells.³⁴ An adequate supply of glycogen in the liver tends to minimize the hepatic damage which may be caused by various injurious agents. Also, the detoxification of various substances by the liver appears to be dependent on an adequate supply of glycogen. Therapeutic application of this by the use of high carbohydrate intake to assure adequate hepatic glycogen content when the liver may be exposed to injury is a common procedure.

The normal liver of a well-nourished individual contains abundant glycogen within the cytoplasm of the hepatic cells. In ordinary sections this gives the cells a foamy or finely reticulated appearance. This is most evident in biopsied liver tissue which is rapidly fixed. Postmortem tissue may show little of this appearance due to glycogen content, except in cases where death was sudden and unexpected. The amount of glycogen present depends on the shortness of the elapsed time between food intake and death. When the agonial period of starvation is long, glyco-

gen in the liver tends to be scanty or absent. The nuclei of liver cells are quite frequently found to be distended by a high glycogen content, which gives them a peculiar clear, vacuolated or glassy appearance.³⁵ Glycogen is particularly likely to be found in the liver-cell nuclei in cases of diabetes mellitus, but its significance in the absence of diabetes is not known (see Fig. 761, page 866). Glycogen is normally quite abundant in various other tissues, such as skin, muscle, parathyroid glands, etc.

Abnormalities of glycogen accumulation and distribution occur particularly in diabetes mellitus, in an inborn error of glycogen metabolism leading to excessive accumulation in certain tissues (glycogen storage disease), and in certain areas of inflammatory reaction or around dead tissues.

Diabetes Mellitus.—Diabetes mellitus inadequately controlled by insulin therapy shows abnormalities in the distribution of glycogen in tissues (see Chapter 30, page 863). The normal store of glycogen in the liver and skin is depleted. In the presence of glycosuria, the epithelial cells of the lower proximal convoluted tubules and Henle's loops show vacuolation due to small globules or larger masses of glycogen. A similar glycogen infiltration of tubular epithelium is seen also in nondiabetic glycosurias.

Glycogen-Storage Disease (von Gierke's Disease).—Glycogen-storage disease is a rare inherent defect of glycogen metabolism, and shows some familial occurrence. As described by von Gierke in 1929, it is a disease of infants characterized by abnormal accumulation of glycogen in the cells of certain organs, particularly liver and heart. There appears to be an impairment of the reversible reaction of conversion of glucose into glycogen and glycogen into glucose. Carbohydrate starvation of tissue leads to increased metabolism of fat and production of ketones. Usually either the liver or the heart is much enlarged by the excessive glycogen storage, but not usually both, so that two distinct forms of the disease occur. The kidneys also are affected in some of the hepatomegalic cases. The cardiac form may be diffuse (a form of congenital cardiac hypertrophy), or may

be localized and in the form of nodular tumorlike masses (see 471).

Hyperglycemia.—There is considerable evidence suggesting that prolonged hyperglycemia causes the structural change of hydropic degeneration and functional injury of the beta cells of the pancreatic islets. The importance of hyperglycemia in the pathogenesis of the degenerative complications of diabetes mellitus is less certain.⁴²

Hypoglycemia.—Hypoglycemia or abnormally low levels of blood sugar may result from injudicious insulin administration. It may occur spontaneously due to excess insulin secreted by a tumor of the islets of Langerhans, or due to other endocrine disturbances. Hypoglycemia also may result from inability to mobilize glycogen as required, due either to depletion of glycogen stores or to glycogen-storage disease. Cerebral symptoms and signs occur with hypoglycemia, probably due to cerebral anoxia, and in fatal cases nonspecific changes are found in the central nervous system. Mild cases may show only edema, congestion, swelling of nerve cells, and occasional thrombi in small vessels. In more severe or prolonged cases, nerve cells show pyknotic, vacuolar, or chromatolytic changes, and there may be gemistocytosis, degeneration of axis cylinders, and petechial hemorrhages.

DISTURBANCE IN METABOLISM OF PROTEINS

Protein Types of Degeneration

Proteins form essential and distinctive constituents of living tissue. No attempt is made here to consider the general subject of metabolism of protein substances, or the effects of excess or deficiency of various amino acids and proteins. However, certain disease processes show disturbance of the condition or quantity of intracellular protein substances, or the appearance of abnormal protein materials in tissue spaces or cells. These conditions include various types of degenerations, such as cloudy swelling or albuminous degeneration, hydropic degeneration, various types of hyaline degeneration, amyloid disease, mucoprotein accumulations, and gout.

Cloudy Swelling.—One of the most frequent, and also often the mildest and most easily reversible of degenerative changes has been termed cloudy swelling, albuminous degeneration, or parenchymatous degeneration. These various names have resulted from the swelling and opaque or cloudy appearance of the affected organs and cells, from the appearance in affected cells of granules of

protein nature, and from the fact that it is the specialized or functioning cells of organs which are affected.

Cloudy swelling results from a variety of injurious conditions. Acute infections or fevers regularly produce cloudy swelling. Certain poisons or toxins, burns, anoxemias, and inanition may be associated with this change. Even sudden excessive demands on an organ, such as on the remaining kidney after unilateral nephrectomy, produce the lesion. It is evident that many different causes acting to disturb cellular metabolism may produce a similar morphologic effect on the cell. The degenerative change varies greatly in severity from a mild and quickly reversible change to a severe degenerative process which proceeds to death of the cell. It should be noted that early autolytic changes in some tissues may simulate the anatomic appearances of cloudy swelling.

While many organs may show changes which may be classed as cloudy swelling, it is best seen in the liver, kidneys, and heart. The affected organ is enlarged, tense, more opaque or cloudy than normal, and may even have a parboiled appearance. The cut surface of the organ bulges or is slightly convex, is grayish, less translucent than normal, and the usual architectural markings tend to be obscured. The degree of change from an appearance normal to the naked eye shows no close correlation with the severity of the microscopic changes. Microscopically, the affected cells are swollen from an increased water content, the cytoplasm is cloudy and granular, and the nucleus is sometimes partially obscured. The granulation may be fine or coarse, and the cytoplasm may even have a foamy or reticulated appearance. It is the more specialized and sensitive parenchymatous cells of an organ that are affected, in the kidney particularly the epithelium of the convoluted tubules, in the liver the cells composing the liver cords rather than those of small bile ducts.

The nature of the change is not entirely clear, and it is not certain that it is the same in all cases. The swelling of the cells is due to increased imbibition of water, apparently the result of some changed osmotic relationship tending to

hold more fluid within the cell. The granules prominent within the cytoplasm appear to be of protein nature, and are soluble in alkalies and in dilute acetic acid. They are coarser than the usual Altmann granules. While it has been claimed by some that the granules are derived, at least in part, from mitochondria, others have failed to find evidence of this origin. Various disturbances in the physical and chemical state of intracellular proteins and changes in intracellular hydrogen-ion concentration have been suggested as possible explanations of the observable morphologic changes.

hydropic degeneration is not common, but is seen in the convoluted tubular cells of the kidney after intravenous administration of hypertonic sucrose solutions (see Fig. 457, page 575). Hydropic degeneration of renal tubular epithelium of somewhat different microscopic appearance results from poisoning by dioxane or diethylene glycol (see Fig. 456, page 574).

Hyaline Degeneration.—Hyalin is a term used for translucent, homogeneous structureless materials which stain with eosin. The term thus describes physical appearances, and is not an indication of chemical composition. However, among

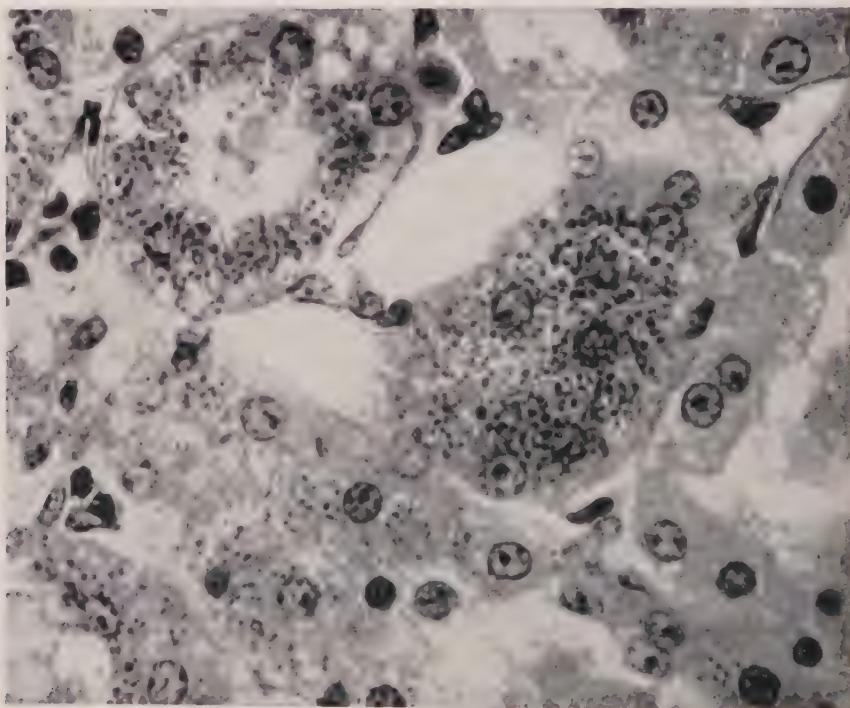


Fig. 62.—Hyaline droplet degeneration of renal tubules.

Hydropic Degeneration.—While in cloudy swelling there is some imbibition of water into the cell, in hydropic degeneration this is of greater degree. The cytoplasm is markedly swollen, pale, clear, and watery, vacuolated or reticulated in appearance. There is no sharp line of distinction between cloudy swelling and mild hydropic degeneration, except that in hydropic degeneration granularity of the cytoplasm does not form a prominent feature. A marked degree of

the variety of hyaline materials, many appear to be of protein nature. Hyalins may be of either connective tissue or epithelial origin. Certain types of hyalin, such as amyloid, are separable from the general group on the basis of certain characteristics or by peculiar staining reactions.

The most common type of hyalin is formed from connective tissue, and is evident in any dense old scar tissue. Hyaline thickening of the splenic capsule

is common in older individuals. Marked hyaline thickening of the pleura may follow chronic inflammation. Some tumors, such as fibromyomas of the uterus, often show hyalin formation. Hyalinization of the walls of blood vessels is a characteristic feature of certain types of arteriosclerosis (page 516). The blood vessels of atrophic organs, such as the ovaries and uterus after the menopause, show prominent hyaline change. In hyalinization of connective tissue, there is apparently a physical change in the fibers, which fuse and lose their individual identity. A similar fusion to form structureless hyaline masses may occur in blood clots, in fibrin masses, and in localized groups of dead cells.

A different type of hyaline degeneration is that in which droplets of eosin-staining material appear in the cytoplasm of epithelial cells. In severe injuries of the kidney, small rounded hyaline droplets often are prominent in the epithelial cells lining convoluted tubules. These hyaline droplets are either products of degeneration produced within the cell, or are protein which has passed through injured and abnormally permeable glomerular tufts, and has been reabsorbed into the tubular cells (see page 574). In alcoholic cirrhosis of the liver, rounded or irregular hyaline masses may appear in the cytoplasm of degenerating hepatic cells (see page 815). A hyaline type of degeneration characteristically occurs in the basophiles of the pituitary in Cushing's syndrome (see page 985). Rounded hyaline masses, known as Russell-Fuchs bodies, are found in degenerating plasma-cell exudates (page 711) in chronic inflammatory lesions.

The hyaline casts seen in the lumina of renal tubules and in urine are composed of coagulated protein. They indicate abnormal permeability of glomeruli to protein, and hence have about the same significance as the presence of albumin in the urine.

Zenker's (Waxy) Degeneration.—Hyaline changes in voluntary muscles were described by Zenker in fatal cases of typhoid fever, and are also seen in other severe infections, such as pneumonia. The degree of the change tends to parallel the intensity of the infection. Bacterial toxins or excess accumulation of lactic acid is probably responsible for the change,

rather than localization of the infection in the muscle. The lesion is best seen in the rectus abdominis. Involvement of the diaphragm is thought to contribute to respiratory difficulties in some cases of severe infections. The involved muscle is very pale and friable, and rupture of the muscle fibers with small hemorrhages often occurs. Microscopically, the affected fibers have lost their striations and have a hyaline appearance. The muscle nuclei are usually absent. In its severer forms, at least, the lesion is a necrosis or death of the muscle fibers, rather than simply a degeneration.

Amyloidosis.—Amyloid is hyalin-like material, apparently of protein nature, distinguishable from other halins by special staining reactions, the site of deposition, and the nature of the conditions in which it occurs. Originally called amyloid because erroneously considered of starchlike nature, the true chemical nature of amyloid is still not known. Variability in staining reactions suggests that amyloid probably is not a single chemical substance, but a series of closely-related protein compounds. It is grossly a structureless translucent material which transmits the color of underlying tissues. Microscopically, it is a hyaline substance which accumulates between parenchymatous cells and in connective tissues.

Four varieties of amyloidosis are commonly recognized, and referred to as (1) secondary, (2) primary, (3) localized amyloid tumors, and (4) amyloidosis with multiple myeloma. Secondary amyloidosis is the most common form and is associated with long-continued, infective, tissue-destructive processes such as tuberculosis, leprosy, osteomyelitis, etc. The organs most often involved are the spleen, kidneys, liver, and adrenals. Blood vessel walls tend to be affected first and most prominently in these organs. Primary amyloidosis, which occurs in the absence of known preceding predisposing disease, tends to involve tissues of mesenchymal origin, rather than the parenchymatous tissues characteristically involved in secondary amyloidosis. Muscle of the tongue and heart are common sites in primary amyloidosis. Solitary amyloid tumors are relatively rare and occur without known predisposing cause. The larynx or other parts of the upper respiratory tract are the most frequent sites. In association with about 7 per cent of cases of multiple myeloma, there occurs amyloidosis similar to pri-

mary amyloidosis in distribution and staining characteristics.

Amyloid is stained by iodine, by the metachromatic dyes, methyl violet and gentian violet, and by congo red. Iodine is most useful in the gross recognition of amyloid deposits, imparting a mahogany-brown color to the amyloid areas. If 1 per cent sulfuric acid is applied after the iodine, a blue color results, although this reaction is inconstant. Methyl violet, best used on frozen sections, stains amyloid a violet color and surrounding tissue blue. Iodine green also may be used, staining the amyloid violet red and remaining tissue green.

in the presence of amyloidosis than in its absence. A dye absorption of 90 per cent or higher is confirmatory evidence of the presence of amyloid disease.⁶³

The amyloid spleen is enlarged, firm, and of rubbery or elastic consistency. On the cut surface the amyloid areas have a characteristic pale translucent appearance. The involvement may be focal or diffuse. In the focal form (sago spleen) the deposition is in arteriolar walls and extends into surrounding lymph follicles. The involved foci are prominently pale and translucent against the red background of the remainder of the spleen. In the diffuse form there is

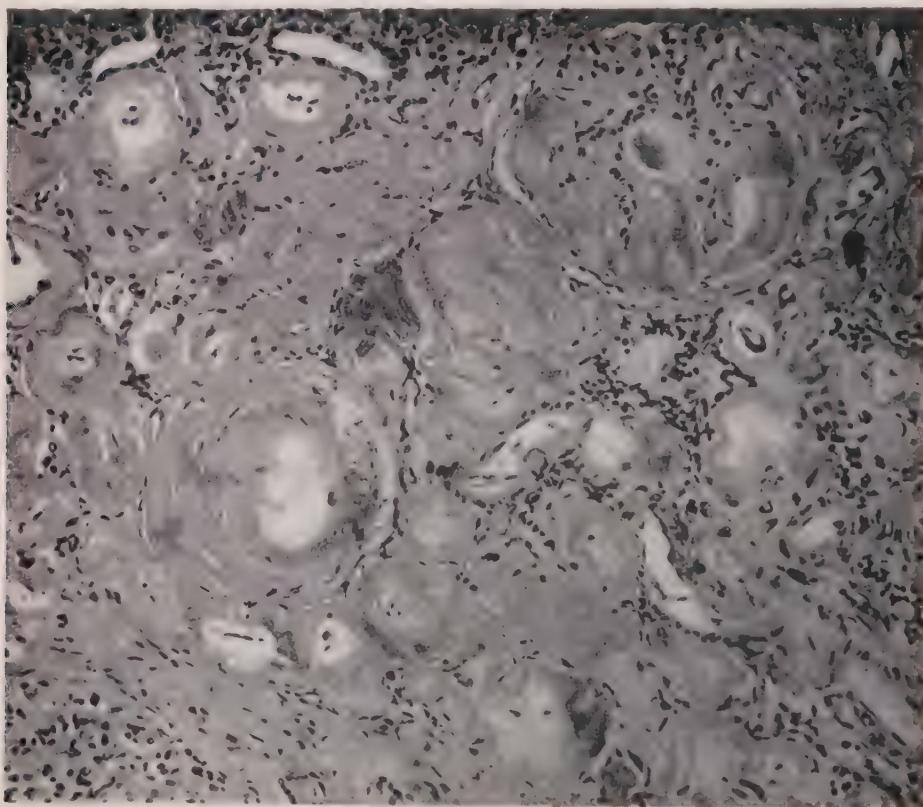


Fig. 63.—Severe amyloidosis of kidney. A glomerulus with considerable amyloid deposit but still recognizable is at the upper right.

Congo red may be used to stain amyloid in tissue sections, but it also is absorbed by amyloid in the living body. This has become the basis of a clinical test for amyloidosis. An aqueous solution of congo red injected intravenously disappears more rapidly from the blood

widespread deposition between the fibrous reticulum of the spleen, the follicles tending to be spared.

In the liver, marked amyloid deposition causes it to be enlarged, firm, and unusually translucent. Deposition tends to occur first in the mid-zonal region of the

liver lobule, appearing in the space between the sinus endothelium and the hepatic cells. In the liver, as elsewhere, the deposition of amyloid tends to cause pressure atrophy of the parenchymatous cells.

Amyloid deposition in the kidney is occasionally severe enough to disturb renal function and give a picture of renal disease. Amyloid is deposited chiefly in glomeruli and blood vessel walls. In the glomeruli the amyloid is deposited between the basement membrane and the endothelial lining of the capillaries. There is interference with the filtering function of the affected glomeruli; the capillaries are narrowed and finally obliterated so that the glomeruli become functionless. Secondary changes occur in the tubules. Occasionally in certain cases the kidney is the only organ showing marked amyloidosis, and in some of these it appears to be primary or without the usual recognized predisposing cause.

Primary systemic amyloidosis is a relatively uncommon condition. It affects particularly individuals of middle age or beyond, develops slowly, and involves especially mesenchymal tissues. Muscle of the heart, tongue, gastrointestinal tract, and media of small blood vessels tend particularly to be affected. Macroglossia and cardiac hypertrophy are particularly common manifestations of primary amyloidosis, and the myocardial deposit appears to contribute to cardiac failure. The amyloid often is variable and atypical in its staining reactions. Deposition in the form of "rings" in fatty tissue may give a distinctive appearance. A reaction on the part of the tissues to the amyloid masses may be shown by foreign-body giant cells and lymphocytic infiltration; such a tissue reaction is uncommon in the usual secondary amyloidosis.

Localized amyloidosis forming tumor-like nodules has been described in many areas, including the respiratory tract (Fig. 583, page 704), tongue, pharynx, thyroid, etc. It is primary, without recognizable preceding causative disease. The hyaline material commonly found in the islets of Langerhans of the pancreas (see page 864) in elderly diabetics appears to be a form of amyloid.

Amyloidosis associated with the multiple myelomas of bones is much like primary systemic amyloidosis in its age incidence, tissue distribution, and variability of staining reaction.

The exact chemical composition of amyloid is unknown. It is insoluble in water, slightly soluble in strong acids, and readily soluble in strong alkalies. Protein fractions and a sulfate-bearing polysaccharide have been identified in its composition.⁵⁸ Amyloid at one time was thought to be a compound of protein and chondroitin-sulfuric acid, but recent observers have failed to identify chondroitin-sulfuric acid in the amyloid, even though it may be present in surrounding tissues.

The causation and mechanism of formation of amyloid is still very much a mystery. An old theory was that amyloid was formed when chondroitin-sulfuric acid, released from the breaking down of cartilage or elastic tissue, combined with protein. Use of chondroitin-sulfuric acid experimentally has not resulted in amyloidosis. In experimental animals, amyloidosis has followed repeated injections

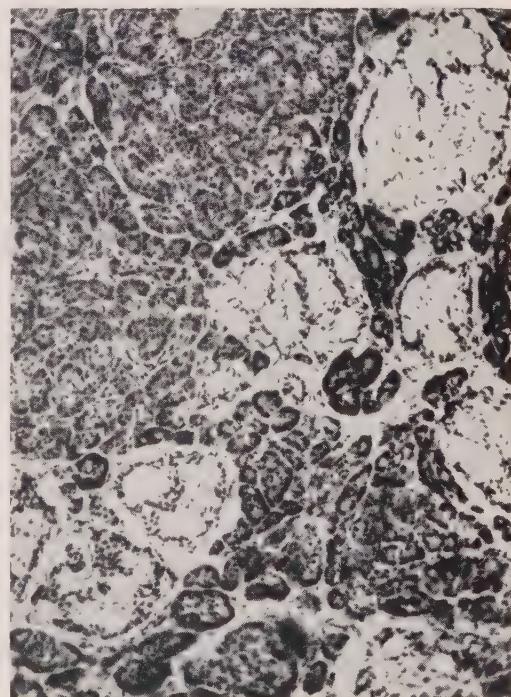


Fig. 64.—Hyalinization of islets of Langerhans of pancreas in diabetes mellitus.

of bacteria, of nutrose (sodium caseinate), and has been reported from excessive feeding of cheese and other proteins in mice, and after hyperimmunization of horses. By some investigators the reticuloendothelial system has been considered to be active in the formation of amyloid. Others have looked upon amyloid as a kind of antigen-antibody precipitate. Some of the conditions in which amyloid is found are characterized by hyperglobulinemia. Little that is definite can be reached in way of conclusion from the evidence, other than that some disturbance of protein metabolism is involved.

tions of mucous membranes. Common examples are the abundant secretion of mucin associated with the common cold, and the thick mucus excreted in inflammations of the large intestine (mucous colitis and dysentery).

Tumors composed of epithelial cells which actively form mucin are termed mucinous carcinomas. Individual cells may be distended with mucin, pushing the nucleus to one side and giving a signet-ring appearance, or the mucin may accumulate in acinar structures. With lack of structural organization in a tumor, the mucin may have no outlet,

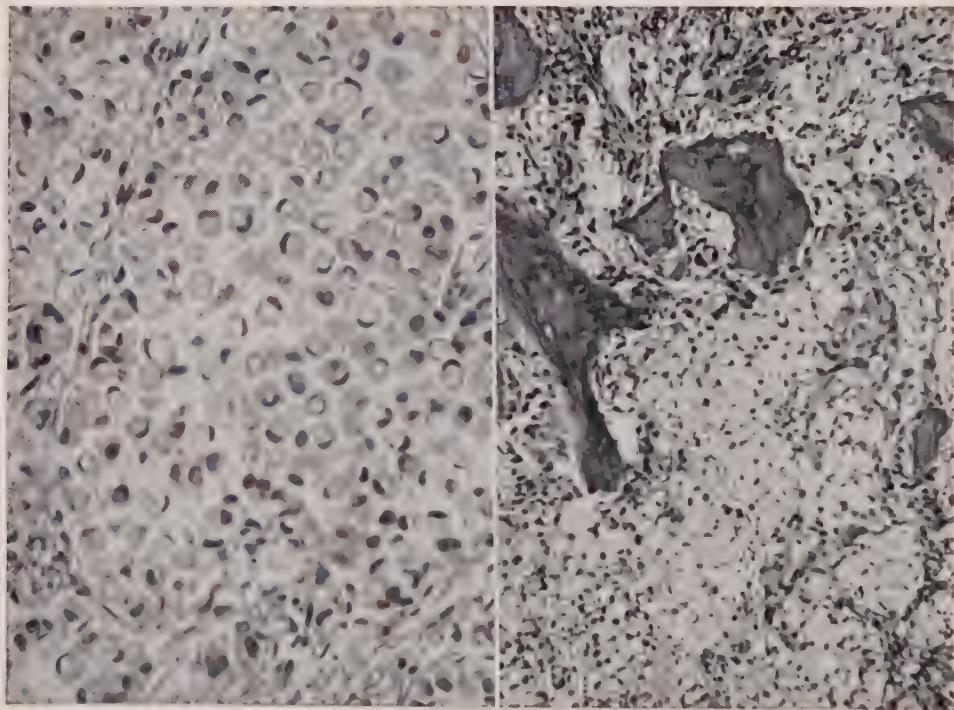


Fig. 65.—Mucinous carcinoma showing "signet ring" cells.

Mucoproteins and Mucinous Degeneration.—Mucin is a structureless, clear, viscid material secreted by epithelial cells lining mucosal surfaces. Composed of both protein and carbohydrate, it is slightly acid and so stains faintly with basophilic stains. A similar material formed by connective tissues, but of slightly different composition and appearance, is called mucoid.

Increased secretion of mucin characteristically occurs in catarrhal inflamma-

and hence may accumulate in large quantities and be associated with degenerative changes in the tumor cells.

An abnormally thick and viscid mucin accumulates in certain conditions. This occurs in the bronchi in asthma, in tracheobronchitis of infancy, and in pancreatic ducts and other areas in fibrocystic disease of the pancreas (see page 850).

Connective tissue mucoid is normally prominent in the umbilical cord. A

pathologic increase of mucoid occurs in the skin and subcutaneous tissues in deficiency of function of the thyroid gland (myxedema, page 1003). Certain connective tissue tumors (myxomas) show abundant mucoid. They are composed of stellate or elongated spindle-shaped cells with fine interlacing processes, between which is the faintly bluish mucoid. Some tumors, such as those of the parotid gland, have certain areas which show this myxomatous appearance. Organizing thrombi in the heart may have a similar myxomatous appearance. Edematous fibrous tumors, such as nasal polyps, may simulate this myxomatous appearance, but the intercellular material usually takes a faint acidophilic stain.

Certain cysts of the ovary accumulate a mucinlike, gelatinous substance or **pseudomucin**. Cysts of the kidney, and occasionally cysts elsewhere, may contain a substance of similar appearance. Pseudomucinous degeneration occurs in the media of the aorta, with the formation of minute cysts.

Colloid is a hyaline, structureless material found within the acini of the thyroid gland, and composed of a protein and iodine compound. It is usually but not always acidophilic. In certain types of goiters (colloid goiters), enlargement of the thyroid gland is associated with excessive accumulation of colloid material. A substance having an appearance similar to colloid but usually without any iodine content is often seen in the pituitary gland, particularly at the junction of the anterior and posterior lobes.

Disturbances of Purine Metabolism

Uric acid is derived mainly from nucleoproteins of food and body tissues, and is produced from purine bases under the influence of specific enzymes. Most of the uric acid is oxidized to urea and excreted as such, only small amounts of uric acid being excreted in the urine. Under pathologic conditions, uric acid is mainly important in the formation of uric acid calculi and so-called "uric acid infarcts" of the kidneys, and in gout.

Gout.—Gout is characterized by deposition of urates in cartilaginous tissues and ligaments about joints, synovia, and tendon sheaths, in the cartilages of the ears and eyelids, in subcutaneous tissues about joints, in heart valves,

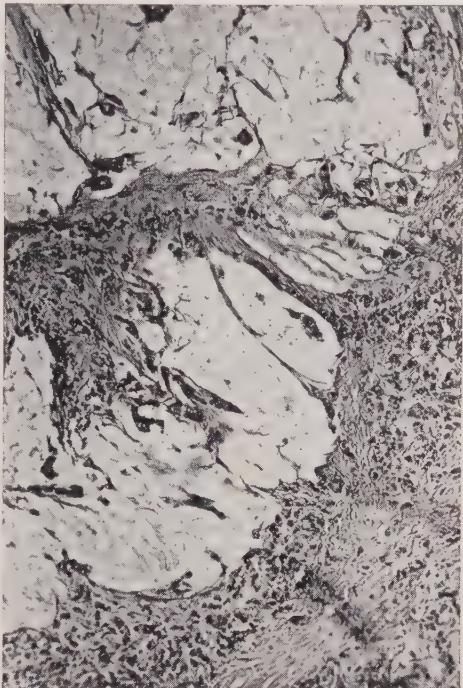


Fig. 66.—Mucinous carcinoma, metastasis in lymph node.

and in interstitial tissues of the kidneys. The deposits form small masses (tophi) which may be visible or palpable clinically. Involved cartilages may be thin, frayed, and eroded, and show whitish plaques at the site of urate deposits. Microscopically, the crystalline masses of sodium urates may be seen, and usually show but little inflammatory reaction around them. Urate deposits may occur in the kidney, and renal disease is common in association with chronic gout.

The exact nature of gout is but poorly understood. It occurs mainly in men of middle age or beyond, and seems to have a familial or hereditary basis. Acute attacks of pain in involved joints are precipitated by exercise of the joint or by overindulgence in rich foods or malted beverages. Lead poisoning also tends to precipitate acute phases of the disease. Uric acid, the end stage of oxidation of purines in man, is present in the blood in increased amounts (up to 10 mg. per 100 c.c.), and gout is often considered to be due to faulty metabolism or faulty excretion of uric acid. However, the exact relationship is not clear, and increased uric acid may be present in individuals and in conditions (uremia, eclampsia) in which urate deposits and gout are not observed.

Urate Deposits in the Kidney.—In many newborn infants and occasionally in adults, urate deposits in the pyramids of the kidneys form yellowish-gray streaks of crystalline material. These have been called "uric acid infarcts," although there is no associated necrosis. The material is uric acid and urates within

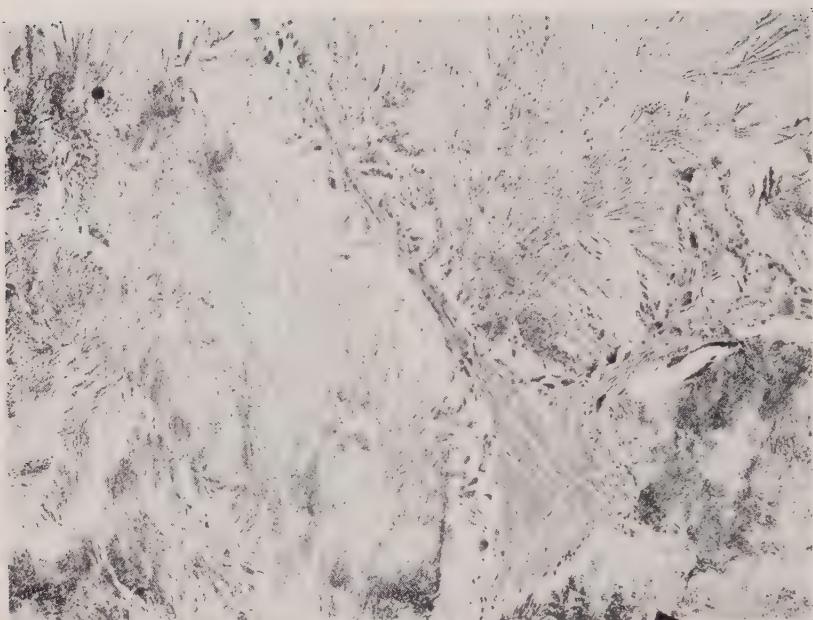


Fig. 67.—Tophus of gout. Massive crystalline deposits, about which there are some multi-nucleated giant cells.

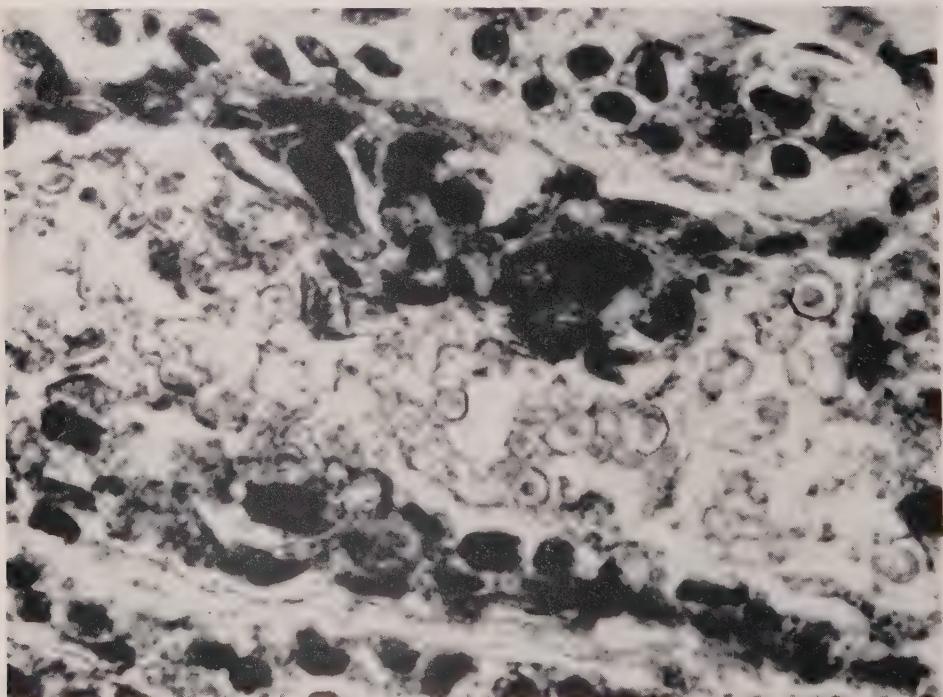


Fig. 68.—Uric acid crystals in renal tubular lumen, from a uric acid "infarct" in an infant's kidney. (AFIP No. 88721.)

the lumens of the collecting tubules. It elicits no inflammatory reaction, and normally is excreted without any damage to the kidney. It appears to be due to the abundant breakdown of nucleoprotein and uric acid excretion in the newborn infant. Diseases in adults in which there is extensive destruction of nucleoprotein (e.g., leukemia, pneumonia, and other cellular destructive conditions) may show a similar effect.

DISTURBANCES OF MINERAL METABOLISM

Various mineral substances play important roles in metabolism of the body, and show disturbance in disease processes. Most of these are not readily demonstrable by gross or histologic methods of examination of tissues, although their role in disease may be important. Most of them will be discussed in connection with the conditions in which the disturbed mineral metabolism is prominent, e.g., disturbed iron metabolism in hemochromatosis (page 82) and in anemias (page 880), disturbed iodine metabolism in goiter (page 997), and fluoride intoxication (page 155).

Calcium and phosphorus are important elements in the body's metabolism, and are normally maintained at certain concentrations within narrow limits in the blood. Important factors in maintenance of normal metabolism of calcium and phosphorus are dietary intake of these elements, vitamin D intake, and parathyroid function. Disturbances due to insufficiency of vitamin D are considered on pages 417 and 1213, and those due to excess of vitamin D on page 417. The effects of dietary deficiency of calcium are considered on page 419. The control by the parathyroid glands and effects of lesions of the parathyroids are noted on page 1017.

Pathologic Calcification.—Calcium salts are normally deposited only in formation of bone and teeth. Pathologic calcification includes all calcium in excretory or secretory passages as well as in tissue proper. In certain soft tissues, however, deposition of calcium occurs with such regularity that it might almost be considered a normal event, e.g., in the pineal after the age of puberty. Particularly important sites of pathologic calcification are blood vessel walls and the kidneys (including formation of renal calculi). All calcium deposits appear to contain calcium phosphate, calcium carbonate,

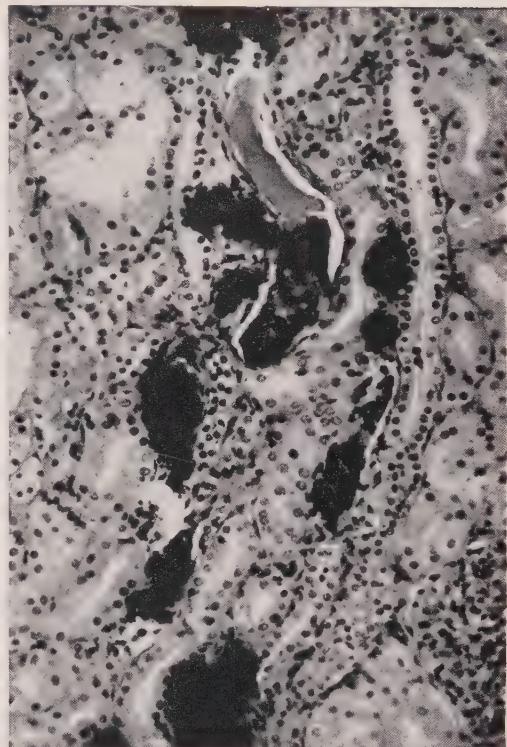


Fig. 69.—Calcium deposit in the kidney. Part of the calcium is interstitial and part intratubular. (From J. Urol. 44: 29, 1940.)



Fig. 70. -Calcification and bone formation in the thyroid.

and variable small traces of other substances. The actual chemical compound present has not been determined with accuracy, and probably is variable, but evidence indicates that it probably belongs to the apatite series of minerals. The chemical composition is similar to that in normal bone.

Pathologic calcification is commonly classified as (1) dystrophic calcification, (2) metastatic calcification, and (3) calcinosis, but it is not possible to make a clear distinction in all cases.

cified (lithopedion). Dystrophic calcification is not dependent upon an increase in the amount of calcium in the blood, but appears to be dependent upon a change in the local condition in the tissues. Local alkalinity in comparison with adjacent undamaged tissue appears to be an important factor initiating the precipitation of calcium in degenerating and dead tissues.

Metastatic calcification is the precipitation of calcium salts in previously undamaged tissues due to an excess in cir-



Fig. 71.—Calcification and bone formation in the kidney.

Dystrophic calcification is the deposition of lime in dead or degenerating tissues. This is the most frequent type of pathologic calcification, and, as any devitalized tissue tends to have calcium salt deposition in it, dystrophic calcification occurs in extremely varied locations. Common sites are in areas of tuberculous necrosis, in blood vessels in arteriosclerosis, in areas of fatty degeneration and necrosis, in degenerating thyroid tissue, in degenerating tumors, and many others. In the case of a retained ectopic fetus, the entire fetus may become cal-

culating blood. It occurs, particularly, due to excess of parathyroid hormone, which depletes the bones of calcium and causes a high level in the blood. It is particularly prominent in those cases in which there are associated damaged kidneys unable to excrete phosphate adequately, so that the phosphate level in the blood is also raised (see page 585). Metastatic calcification also may result from hypervitaminosis D, and from destructive bone lesions, particularly tumors. In metastatic calcification, the calcium deposits tend to occur mainly in the kid-

neys, lungs, gastric mucosa, and media of blood vessels. It has been postulated that the kidneys, lungs, and gastric mucosa are predisposed to calcium precipitation by the relatively alkaline state which follows their excretion or secretion of an acid substance. In addition, any degenerated or necrotic tissue tends to become infiltrated by calcium when the circulating calcium level is increased, the factor of dystrophic calcification thus being present also in many circumstances. Alkaline phosphatase appears to be active in the calcification of living or recently necrosed tissue, but not in the calcification of hyaline connective tissue.⁸⁶

Calcinosis is a condition of calcification in or under the skin. A circumscribed form (*calcinosis circumscripta*) and a generalized form (*calcinosis universalis*) have been described, the latter having a wider distribution of lesions, including often tendons, fasciae, muscles, and nerves, and more severe general symptoms. It is sometimes associated with scleroderma (see page 1148).

Pathologic Ossification.—In pathologic ossification, unlike simple calcification, there is formation of bone structures such as lamellae, lacunae, and sometimes marrow. Heteroplastic formation of bone may occur in almost any tissue, such as eyes, kidneys, muscles, heart valves, myocardium, aorta, lungs, pleura, etc. Calcification is probably a necessary precursor. Granulation tissue forms around the calcium deposit, some of the connective tissue cells acting as osteoblasts. An injured eye with chronic inflammation is particularly likely to have heteroplastic bone formation in it (see page 717).

Myositis ossificans occurs in a localized form following trauma to a muscle, and as a progressive widespread form in which there occurs calcification and ossification of muscles, tendons, fasciae, and ligaments.

DISTURBANCES IN PIGMENT METABOLISM

In a number of conditions, colored materials are deposited in the skin or internal tissues. Although considered here together, many of these conditions of pigmentation have nothing in common except the pigment deposition. There are two classes of pigmentation: (1) endogenous pigmentations in which the colored substance is produced within the body, and (2) exogenous pigmentations, in which the pigment is introduced into the body by way of the intestinal tract, skin, or lungs.

Endogenous Pigmentations

There are three main types of pigments produced in the body: melanins, hemoglobin derivatives, and lipochromes.

MELANIN

Melanin forms the normal coloring material of the skin and choroid coat of the eye. It is produced in the skin by melanoblasts, situated in the basal layers of the epidermis. These specialized cells may be distinguished, even though they contain no pigment at the time, by the "dopa" reaction (see page 1166). Pigment-carrying cells (melanophores) are present in the subepithelial tissues. The amount of melanin in the skin is increased by exposure to sunlight. The amount of skin pigmentation varies in individuals and in different races.

Pathologic increase of skin pigmentation occurs in many conditions. It is characteristic of Addison's disease (see page 1034) due to destruction of the adrenal cortices. Increased skin pigmentation in hemochromatosis (page 82) is in part due to iron-containing pigments as well as to increase of melanin. Localized pigmented spots (*café-au-lait* spots) are common in association with multiple neurofibromatosis and in fibrous dysplasia of bone (Albright's syndrome). Localized increased pigmentation occurs in pregnancy, and sometimes with other uterine or ovarian conditions (chlorasma).

Patchy areas lacking in pigment are common (vitiligo or leucoderma). Congenital deficiency or absence of normal melanin pigmentation occurs in the condition known as albinism. Scarred areas of the skin often remain deficient in pigment. Irregular patchy areas of skin depigmentation result in the spirochetal disease, *pinta* (see page 281), and occur in leprosy in areas affected by nerve involvement.

Benign pigmented nevi and malignant melanomas are tumors composed of melanoblasts. The amount of pigment in such tumors shows great variations. Skin pigmentation and the melanotic tumors are considered in greater detail in Chapter 41, pages 1153 and 1165.

Ochronosis.—Ochronosis is a rare type of pigmentation by a melanin, in which cartilage is affected. Discoloration of the subcutaneous cartilages of the ear and of the nose may be visible through the skin, imparting an ochre color. Most cases are due to a congenital metabolic disturbance evidenced by alkapturia. Pigmentary derivatives in the urine give it, on standing, a brownish-black color due to the presence of homogentisic acid. Phenol poisoning, due to absorption of phenol from surgical dressings, has been reported to cause a pigmentation similar to ochronosis.

Melanosis Coli.—Melanosis coli is a brown or black discoloration of the mucosa of the appendix or large intestine due to a melanin-like pigment held in large mononuclear cells. The pigment may also be found in the submucosa, and sometimes in mesenteric lymph nodes. Stasis of intestinal contents due to constipation or chronic obstruction is believed to promote ab-

sorption of protein disintegration products which then are converted into pigment by a tyrosinase-like ferment.

HEMOGLOBIN-DERIVED PIGMENTS

Hemoglobin, the pigment of red blood cells, is a combination of a pigment complex, *heme*, plus a protein, *globin*. Three main varieties of pigment may be formed from hemoglobin breakdown: hemosiderin, bilirubin (hematoidin), and hematin.

Hemosiderin.—Hemosiderin is a brownish granular pigment formed when hemoglobin breaks down in tissues (e.g., as the result of hemorrhage). Hemosiderin is formed within the phagocytic cells of the reticulo-endothelial system, and the time required for its production may be as short as one day. Hemosiderin has no exact chemical composition, but contains loosely bound iron which gives a Prussian blue reaction (a blue color with potassium ferrocyanide and hydrochloric acid). The iron is present mainly in the ferric form.

The normal continuous breakdown of red blood cells in the reticuloendothelial

system results in some deposition in the liver and spleen. Pathologic excess of hemosiderin deposit occurs in these organs and elsewhere whenever there is excessive breakdown of blood. Such occurs in local areas of hemorrhage, in hemolytic anemias (e.g., pernicious anemia, sickle-cell anemia), and in passive congestion of organs where stagnation in capillaries results in increased blood destruction. In the spleen, hemosiderin pigment is found in phagocytic cells of the pulp and sinuses. In the liver, the pigment is found both in the phagocytic Kupffer cells of the sinusoids, and in the liver cells. In the kidney, tubular lining cells, as well as interstitial tissue and endothelial cells, may contain pigment. In the lung, hemosiderin pigment is often abundant in large mononuclear phagocytic cells in alveoli, when there is chronic congestion. These pigmented alveolar macrophages are often called "heart failure cells" because of their association with circulatory failure. In the spleen in some cases of sickle-cell anemia, Banti's disease, and other congestive splenomegalias, very marked hemosiderin deposits associated with fibrotic nodules may occur. Connective tissue fibers become encrusted with iron-containing pigment.

Hemochromatosis.—Hemochromatosis is a rare disturbance of iron pigment metabolism, usually occurring in males past middle life. It is characterized by excessive hemosiderin pigmentation of the skin and viscera, particularly liver and pancreas, with associated fibrosis of involved viscera. In some cases the pancreatic fibrosis is sufficient to cause functional disturbance and diabetes mellitus is co-existent. Such cases have been labeled "bronzed diabetes" (see page 865). While the pigment is predominantly hemosiderin, some yellowish pigment, hemofuscin, may be present as well. Fibrosis in the liver is primarily about portal areas, but later becomes widespread and associated with atrophy of liver cells (pigmentary cirrhosis, see page 818). Pancreas, spleen, and lymph nodes also commonly become pigmented and fibrosed. Affected organs have a deep brown color. Lesser degrees of pigment deposit occur in the thyroid, adrenal cortices, and other organs. The

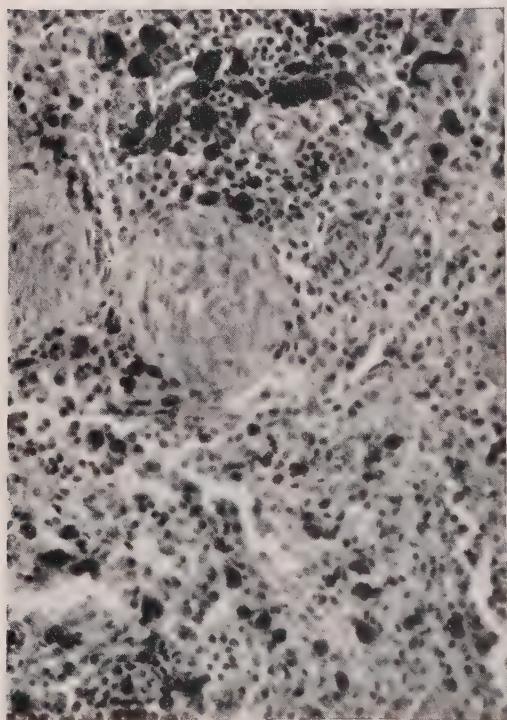


Fig. 72.—Hemosiderin pigment in spleen.

total amount of iron in the body, normally about 4 grams, may be increased as much as twelve times. The skin pigmentation is distinguishable on biopsy from other types by the presence of the iron-containing pigment which gives a Prussian blue reaction. However, there is usually increased melanin in the skin as well, accounting, at least in part, for the bronzing.

The exact etiology of hemochromatosis is not clear. The predominance in males, the rare occurrence before middle life, the accumulation of pigments other than hemosiderin, and other evidence has suggested that it is fundamentally a metabolic disturbance, or disorder of metabolism of iron in the cytochrome system. It has been suggested that there is some inborn inability to utilize certain iron compounds, which gradually accumulate in the tissues as hemosiderin, and eventually promote fibrosis. Recent evidence has suggested that there may be an increased absorption of iron, small in quantity but over a long period of time. The metabolic error may be due to abnormality of the mucosal cells which govern iron absorption, or to a greater reducing tendency of the cells for iron. Most studies of hemochromatosis have failed to find evidence of increased blood destruction, but a variety of hemochromatosis may result from administering a large number of transfusions to a patient with hemolytic anemia (transfusional siderosis, exogenous hemochromatosis). Toxins and metallic poisons such as copper, zinc, and lead have been suggested as possible etiological factors, but there is insufficient evidence of their importance in causation. The diabetes mellitus which develops is usually of mild degree, but may be quite resistant to insulin therapy, probably on account of the associated hepatic damage. The cirrhotic changes in the liver frequently are sufficient to give rise to obstruction of the portal circulation, and the associated effects of ascites and esophageal varices. Primary carcinoma of the liver has been a terminal complication of about 7 per cent of reported cases.

Bilirubin and Hematoxin.—Bile pigment is formed from the breakdown of hemoglobin by reticulo-endothelial cells, particularly in the spleen, liver, and bone marrow. Excessive bilirubin in the cir-

culation causes the yellowish pigmentation known as jaundice or icterus.

Hematoxin is a pigment, closely related to, or identical with, bilirubin and formed in tissues from hemoglobin. Like hemosiderin, its formation is intracellular, but several days are required to produce hematoxin. It is formed mainly in tissues wherein a good oxygen supply is lacking. Hence it is often found where there is breakdown of blood in dead or dying tissues, as in infarcts. Hematoxin may be seen as amorphous yellow granules, or sheaves of crystals. It does not give the Prussian blue reaction for free iron, but does give the Gmelin reaction for bile.

JAUNDICE*

Jaundice, or icterus, is the condition in which there is hyperbilirubinemia and deposition of bile pigment in the tissues of the body. It is manifested clinically by a yellowish to orange or even greenish discoloration of the skin, scleras, and mucous membranes.

Mechanism of Formation and Excretion of Bile Pigment

The formation and excretion of bile has engaged the interests of medical men since before the time of Hippocrates. It was long assumed that bile pigment was not only excreted, but also manufactured by the liver. Virchow was the first to hold that bile pigment was formed elsewhere in the body. He demonstrated a pigment, "hematoxin," at the site of old hemorrhages, which had the physical and chemical characteristics of bilirubin. The concept of the extrahepatic formation of bile pigment was not generally accepted, however, principally because of the experiments of Minkowski and Naunyn. These investigators demonstrated that no new bile pigment appeared in the blood stream of a goose after complete extirpation of the liver. It was not until almost thirty years later that this experiment was satisfactorily explained, when it was shown that almost the entire reticulo-endothelial system of a goose is concentrated in the liver. When the liver is removed, the manufacturing, as well as the excreting, tissue is ablated. Dogs, like man, have only a minor portion of the reticulo-endothelial system in the liver and show a marked immediate hyperbilirubinemia when the liver is completely removed. It is now generally accepted that in man the production of bilirubin from hemoglobin is largely by extrahepatic portions of the reticulo-endothelial system.

It has been shown repeatedly that injected hemoglobin is quantitatively changed to bilirubin and excreted in the bile. The steps involved are of fundamental importance in the study of jaundice, since jaundice of any type is merely an outward manifestation of an abnormality in one or more phases of this transition. It was

*The discussion of jaundice is contributed by Dr. R. S. Haukohl.

believed, until recently, that hemoglobin was first changed to hematin by the splitting off of its protein fraction, globin. This was thought to be true because of the relative ease with which hematin may be formed in the test tube by the addition of either acid or alkali. The next step was assumed to be the splitting of hematin into an iron-containing fraction, hemosiderin, and an iron-free fraction, hematoidin or bilirubin. However, it has been shown that, although a somewhat similar breakdown of hemoglobin occurs in certain pathologic states, notably blackwater fever, severe liver disease, and gas bacillus sepsis, hematin does not normally occur in the transition to bilirubin. Injected hematin is converted to bilirubin very slowly, lagging behind the rapid transition from hemoglobin. The transition from hemoglobin to bilirubin is, in fact, over an entirely different pathway.

Hemoglobin is composed of four molecules of the ferrous complex of protoporphyrin and one molecule of the protein, globin. The porphyrins, in one form or another, are the basic respiratory pigment of most animal and plant life. The ferrous complex of protoporphyrin, without protein linkage, has been designated as "heme." The first step in the transition to bilirubin is the opening of the porphyrin ring, at a particular point, with the formation of what has been termed "verdohemoglobin" or "green hemoglobin," a biliverdin-iron-globin. Five to eight per cent of the circulating extracellular hemoglobin has been shown to be of this type. Iron, which is tightly bound in the original hemoglobin molecule, is easily split off from this form. The liberated iron travels, thenceforth, with the globulin fraction of the serum proteins, while bilirubin remains with the albumin fraction. These changes are brought about in the reticuloendothelial system. The resulting protein-bilirubin complex is carried to the liver in the blood stream. Here it is liberated from its protein linkage by the polygonal cells and excreted in the bile.

There are fundamental and important differences between the bilirubin normally found in the circulating blood and that excreted in the bile. These were first demonstrated by van den Bergh. He showed that when serum containing bilirubin which has been acted upon by the liver, as in obstructive jaundice, is treated with a diazotizing reagent, a bluish-violet color develops immediately (direct immediate reaction), or after one to fifteen minutes (direct delayed reaction). This reaction cannot be obtained with normal serum, or with serum containing an increased quantity of bilirubin which has not been acted upon by the liver. To obtain the characteristic color which will demonstrate this prehepatic bilirubin, it is necessary to treat the serum with alcohol, as well as with the diazotizing reagent (indirect reaction). The prehepatic bilirubin which gives only the indirect reaction is insoluble in water and cannot be excreted by the kidney regardless of the blood level (acholuric jaundice). On the other hand, bilirubin which gives the direct reaction is readily soluble in water and is excreted in the urine.

These easily demonstrable differences in bilirubin have provoked considerable specula-

tion, and also productive research. The most probable explanation, in keeping with the findings of Coolidge¹⁰⁰ and Watson,^{101, 102} is related to the nature of the protein attachment. As previously stated, the normal bilirubin of the blood is found with the albumin fraction of the serum proteins. This, however, does not mean that it has been separated from the original globin of the hemoglobin molecule. It is probable that the bilirubin is not chemically attached to the serum albumin but rather incidentally found with this fraction still in combination with globin. The two proteins display similar ultracentrifugal and electrophoretic behavior. Indeed, some investigators have questioned the occurrence of the specific protein, globin. Coolidge¹⁰⁰ has shown the bilirubin-protein attachment to be by actual valence bonds. In the indirect van den Bergh test, alcohol probably acts as a catalyst breaking down the attachment and allowing the bilirubin to react with the diazo reagent. On the other hand, direct-reacting bilirubin, when present in the blood stream, is only loosely attached to protein in an easily dissociable complex. The polygonal cells of the liver divest the indirect-reacting bilirubin, "bilirubinglobin," of its protein and pass the pigment on into the bile canaliculi. Here it is probably converted into a salt, sodium bilirubinate, in the weakly alkaline bile.

Bilirubin, excreted as the normal pigment of bile, is changed within the bowel, principally by the action of the intestinal bacterial flora, to the brown pigment of the stool, urobilin. Some of the steps in this transformation are of clinical and pathological importance. Bilirubin undergoes several simple reductions, first, to mesobilirubinogen and then, by the interaction of certain bile and fecal factors, to sterobilinogen. The differences between these two chromogens are of no known physiological or clinical significance. They are, perhaps, best thought of as a single substance, urobilinogen, since they are quantitated as one by the Ehrlich reaction. Similarly, the pigments resulting from the oxidation of these chromogens, sterobilin, urobilin 9 α , and d-urobilin, are best referred to as single substance, urobilin. We may then simply say that bilirubin is reduced to the colorless chromogen urobilinogen, by the intestinal bacteria, and ultimately oxidized to the fecal pigment urobilin. Although most of the urobilinogen is excreted in the stool, unchanged or as urobilin, a certain percentage is normally reabsorbed from the bowel. It is transported via the portal system to the liver, where it is re-excreted in the bile. A small amount escapes into the systemic circulation and is removed by the kidneys. The amount of urobilinogen reabsorbed from the bowel is usually roughly proportional to the amount of bilirubin entering the intestinal tract, a fact of considerable moment in the clinical interpretation of certain forms of jaundice. The ability of the liver to re-excrete urobilinogen is one of the most sensitive of its many functions, and is among the first to fail in hepatic disease. Since the chromogen is readily excreted by the kidney, tests for the presence of urobilinogen and urobilin in the urine are of obvious clinical importance in the differential diagnosis of jaundice.

Mechanisms of Jaundice

Keeping in mind the normal metabolism of bilirubin, a number of possibilities suggest themselves as underlying mechanisms of jaundice: (1) Bilirubin may be formed more rapidly than the liver can excrete it. (2) The hepatic threshold for the excretion of bilirubin may be elevated as a result of an inherent congenital defect, so that pigment produced at a normal rate cannot be completely removed from the blood. (3) The excretory mechanism of the hepatic cells may be disturbed as a result of actual disease. (4) The alteration of hepatic cells may be of such a degree that they not only are unable to remove bilirubin from the blood stream, but also allow the regurgitation back into the sinusoids of bile already excreted. (5) The biliary tree may be obstructed at almost any level, preventing the drainage of bile into the intestinal tract and causing a damming back into the blood stream. Little need be said in amplification of the fourth and fifth possibilities. In regard to the first, it has been shown that the normal liver is capable of removing enormous quantities of bilirubin from the blood, rapidly enough to prevent clinical jaundice. With this marked normal reserve it would seem that the additional factor of damaged hepatic cells must be present before jaundice can occur as a result of any ordinary hemolytic conditions. This has been shown to be the case in diseases formerly thought of and classified as "hemolytic jaundice." Although the second mechanism listed above does not appear probable, and its occurrence is disputed by some, a few cases said to be of this type have been described under the designations of constitutional hepatic dysfunction and familial nonhemolytic jaundice.

Classification of Jaundice

The majority of clinical classifications of jaundice are based upon the grouping devised by McNee.¹⁰³ McNee classified jaundice into three principal types: (1) hemolytic, (2) toxic or infective, and (3) obstructive. In the light of the foregoing, this classification is obviously unsatisfactory. It lumps together widely divergent clinical and pathologic types, provides no satisfactory place for the jaundice of chronic passive congestion, and shows no common basis of classification, i.e., two groupings are based on pathogenesis and the third on etiology. On the other hand, a method of classification proposed by Rich appears to be the most practical and clinically valuable. It is based entirely on pathogenesis. Rich¹⁰⁴ divides jaundice into but two large groups, retention jaundice and regurgitation jaundice.

In retention jaundice the defect in bilirubin metabolism lies in the inability of the liver cells to remove an increased,

TABLE I
DIFFERENCES BETWEEN THE TYPES
OF JAUNDICE

	RETENTION JAUNDICE	REGURGITATION JAUNDICE
Van den Bergh reaction	Indirect	Direct
Stool	Increased uro- bilinogen and urobilin	Decreased or absent bilirubin, hence de- creased uro- bilinogen and urobilin
Urine	Increased uro- bilinogen and urobilin	No urobilinogen or urobilin
	No bilirubin or bile salts	Bilirubin and bile salts present

or sometimes normal, amount of pigment from the blood stream. The bilirubin present is of the indirect reacting type and, therefore, is not excreted by the kidneys (acholuric jaundice). The amount of bilirubin present in the intestinal tract, and hence the amount of urobilinogen and urobilin in both stool and urine, are usually increased. With regurgitation jaundice, on the other hand, there is a leakage or regurgitation of bile back into the blood stream. The bilirubin involved has been acted upon by hepatic cells. Depending on the particular pathogenetic factors this may be due to either an increased intrabiliary pressure with actual disruption of the bile capillaries, or to an increased permeability of these structures resulting from damage. In this type of jaundice the van den Bergh reaction is usually direct, and variable quantities of bilirubin are present in the urine. The color of the stool will depend upon the amount of bilirubin reaching the intestinal tract. The more important causes of jaundice may then be classified, after Rich, as follows:

I. Retention jaundice, due to

A. Anoxemia, caused by

1. Anemia:

- a. Hemolytic anemias—familial or acquired hemolytic jaundice, sickle cell, and pernicious anemia, erythroblastosis fetalis.

- b. Hemoglobinemias—mismatched trans-fusions, paroxysmal hemoglobinuria.
 - c. Certain hemolytic drugs.
 - 2. Chronic passive congestion.
 - B. Febrile disease, associated with anoxemia, resulting from
 - 1. Anemia—hemolytic septicemias, malaria, and blackwater fever.
 - 2. Pulmonary consolidation—pneumonia.
 - C. Immaturity of liver cells in newborn—*icterus neonatorum*.
 - D. Constitutional hepatic dysfunction.
- II. Regurgitation jaundice, due to**
- A. Necrosis of liver cells, caused by
 - 1. Severe grades of hepatic cell anoxemia.
 - 2. Toxic agents:
 - a. Poisons—chloroform, phosphorus, mushroom poisoning, etc.
 - b. Organisms—viral hepatitis, yellow fever, Weil's disease, congenital syphilis, etc.
 - c. Undetermined—"idiopathic" acute yellow atrophy.
 - B. Obstruction of biliary tree, caused by
 - 1. Plugging—calculi, parasites, neoplasms, etc.
 - 2. Stricture—congenital scarring, neoplasms, etc.
 - 3. External pressure—inflammatory, neoplastic or parasitic masses.

Effects of Jaundice

Although jaundice by definition relates to but the accumulation of excess bile pigment in the blood stream and tissues, and the effects of this accumulation comprise the easily observable clinical and pathologic findings, the retention of bilirubin of itself is perhaps of little importance. In the patient with a pure retention type of *icterus* there is little disturbance other than discoloration of the skin. On the other hand, the secondary effects in regurgitation jaundice are profound. This is due to the additional regurgitation of bile salts and to the absence of these substances from the intestinal tract. It has been repeatedly demonstrated that the bile salts, sodium glycocholate and sodium taurocholate, are manufactured and normally excreted solely by the liver. Under pathological conditions, when they appear in the systemic circulation, they may be excreted by the kidney. Normally, a considerable percentage of the bile salts is reabsorbed from the intestinal tract and re-excreted or detoxified by the liver, acting as a natural cholagogue. The action of bile salts in reducing surface tensions within the intestinal tract is essential for the proper digestion and absorption of fats and fat soluble vitamins.

With regurgitation jaundice, it is the bile salt and not the pigment that causes marked pruritus. The effects of bile salts on the central nervous system are responsible for the nervous symptoms so often accompanying jaundice, and probably for the marked bradycardia. The fatty stools and the marked bleeding tendency with obstructive jaundice are manifestations of the absence of bile salts from the intestinal

tract. The bleeding tendency has received particular attention in recent years. With the absence of the bile salts, fat-soluble vitamin K is not absorbed. Without this vitamin, prothrombin cannot be formed and the deficiency is manifested clinically by a hemorrhagic diathesis with a prolonged prothrombin time.

The accumulation of bile salts in the blood stream, however, is not sustained, as is hyperbilirubinemia, since the salts are not only excreted but also formed by the liver. After a variable period, depending upon the degree of hepatic damage, the liver no longer manufactures the substances, and the accumulated bile salts are eliminated by the kidneys. This raises a question as to whether the bile salts themselves or some other unknown substances not detoxified by a damaged liver may be responsible for the severe nervous manifestations and other systemic symptoms.

The renal lesions associated with jaundice (cholemic nephrosis) are discussed on page 575.

Hematoporphyrinuria.—Hematoporphyrin is a pigment normally found in minute amounts in the urine. In a rare inborn disturbance of hemoglobin metabolism, congenital chronic hematoporphyrinuria, large amounts of porphyrins, uroporphyrin and coproporphyrin, are found in certain tissues and are excreted in the urine, which is colored Burgundy red. It appears to be familial, and red urine is present from birth. It is more common in males. Dentine of the teeth and the cortex of bones are pigmented from porphyrin deposit, and other organs also may show pigmentation. Individuals having this disease are abnormally sensitive to light, exposure resulting in inflammatory lesions of the skin and conjunctiva.

Acute porphyrinurias occur due to drugs such as sulfonal and trional, and also idiopathic cases. Such cases are mainly in adult life and mostly in females. Pigmentation of bones and teeth, and photosensitivity are absent.

Hematin and Malarial Pigment.—Hematin, which may be formed by the action of acids or alkalies on hemoglobin, is not a normal breakdown product of hemoglobin, nor a precursor of hemosiderin and bile pigments. However, Fairley⁹⁸ has indicated the possibility of its formation in some cases of intravascular hemolysis or hemoglobinemia. In such cases it rapidly combines with blood proteins to form methemalbumin. In the tissues, hematin appears as a brownish granular pigment resembling hemosiderin. However, its iron is firmly bound, so that it fails to give a Prussian blue reaction as does hemosiderin.

In massive hemoglobinurias such as may result from transfusion reactions, casts of hematin pigment may be formed in renal tubules by the action of an acid urine and are a contributing factor in the resulting renal failure.

Malarial pigment is a closely related (hematin) compound formed by action of the malarial parasite on the hemoglobin in the red blood cell. Massive deposits of this brown pigment, which fails to stain for iron, are formed in reticulo-endothelial cells of spleen and liver.

Chloroma.—Chloroma is a rare tumor of green color occurring in cases of myeloid leukemia. The green color of the tissue fades from oxidation on exposure to air, but may be maintained or restored by keeping the specimen in a solution containing a reducing agent such as sodium hydrosulfite. The green pigment has often been considered a lipochrome, but there is evidence that it is an abnormal breakdown product of hemoglobin similar to choleglobin derivatives.¹⁰⁶

LIPOCHROME PIGMENTS

Lipochromes are yellowish pigments which are soluble in fat solvents but do not stain with the usual fat stains. They are normally present in the corpus luteum, testis, adrenal cortex, ganglion cells, fat, and other tissues. Carotene, a vegetable pigment ingested with food, is probably related to the lipochromes. Certain lipochromes, increasing in abundance with age, have been looked upon as the result of wear and tear of tissues. The pigments at the nuclear poles of myocardial fibers in brown atrophy of the heart have been considered lipochromes, but there is evidence that such pigment is mainly hemoglobin-derived.

Ceroid.—Ceroid is a greenish-yellow pigment found in the liver in experimental dietary cirrhosis in animals. The pigment, although insoluble in fat solvents, stains with fat stains, with basic aniline dyes (especially methyl green), is acid-fast with the Ziehl-Neelsen method, and is fluorescent. The nature and significance of this pigment is uncertain, but evidence has been presented suggesting a relationship to vitamin E deficiency.¹¹⁰

Exogenous Pigmentations

Colored materials may gain entrance to the body by inspiration, ingestion, and inoculation into the skin. Pigmentation of the lung by inspired substances such as carbon forms an important group of pulmonary conditions known as the pneumoconioses. The most important forms are due to coal dust (anthracosis), to silicon dioxide (silicosis), to iron dust (siderosis), and to asbestos fibers (asbestosis). Anthracosis, the most frequent form, which is almost universal in civilized communities, causes little or no inflammatory reaction or fibrosis in the lung, nor does it appear to predispose the lung to other disease processes. In silicosis, siderosis, and asbestosis, on the other hand, serious disturbance is caused by the presence of the dust. The pneumoconioses are considered in detail on page 660.

Metallic poisons on ingestion or absorption may cause pigmentation of the skin and other tissues (see page 1153). The most important are silver and lead.

Silver poisoning or **argyria** may follow absorption of either organic or inorganic silver compounds. Pigmentation occurs in the oral mucous membranes and the skin, the skin acquiring a permanent ashen-gray hue of unpleasant appearance. The pigment, an insoluble albuminate of silver, is deposited in the upper layers of the corium, immediately under the epithelium and around sweat and sebaceous glands. It appears to be deposited in the cement substance between cells, and along and between bundles of collagenous and elastic fibers. Only small amounts are held in the cytoplasm of phagocytic cells. In severe cases the pigment is present in the kidney and liver as well. In the kidney the deposit occurs in the basement membrane of the glomeruli. No cellular reaction is induced by the silver, and no injury is produced other than the pigmentation.

Lead poisoning (plumbism) may cause pigmentation of the oral mucosa. A line of deep blue pigmentation develops at the junction of the teeth and gums, due to the formation of lead sulfide.

Tattoos are pigments introduced into the skin by a needle or other sharp instrument for decorative purposes. The pigment may be seen as small granules held in the corium by macrophages. Infections, such as syphilis and in-



Fig. 73.—Argyria. Granular particles of silver in the subepidermal layer of the cutis. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.) (From Wiener, Skin Manifestations of Internal Disorders, The C. V. Mosby Co., 1947.)

fectious hepatitis, may be introduced at the time of tattooing by unclean habits of the operator.

NECROSIS

The most serious effect of injury is death, which may be of the body as a whole (somatic death), or of circumscribed localized areas of tissue or certain cells. Circumscribed cell or tissue death within the living body is termed necrosis, and is recognizable by the changes which the dead tissues and cells undergo after their death. The term necrobiosis has been used in reference to the physiologic death and replacement of certain cells which is constantly occurring, e.g., blood cells and in epidermis. The term has also been used to refer to the severe degenerative changes which eventually terminate in death of the cells.

Necrosis may be caused by almost any type of severe injury. Physical agents such as trauma, heat, and radiant energy may cause death of cells. Various chemical poisons, both exogenous and endogenous in origin, cause necrosis, and often selectively act upon certain cells or tissues. Mercury tends to cause necrosis of renal tubular cells, chloroform of central cells of hepatic lobules, phosphorus of peripheral cells of the hepatic lobule, etc. Interference with nutrition of tissues due to deficiency or interruption of circulation is a frequent cause of death of tissues (ischemic necrosis). Various pathogenic organisms characteristically cause necrosis, sometimes of distinctive type.

Macroscopic areas of dead tissue tend to be opaque, i.e., the normal translucency of most living tissues is lost, and a whitish or yellowish color is assumed. However, gross appearances of necrotic tissue may differ, varying with the type of tissue affected and the causative agent, so that several types are described.

Coagulation necrosis is a type commonly produced by cutting off of blood supply, i.e., in infarction, and is characterized by a protoplasmic coagulative process. In such necrosis, general architectural features may be preserved for a considerable period, although cellular detail is lost. Small amounts of fibrin or of fibrinoid material are seen microscopically in the necrotic areas.

Caseous necrosis is so-called because of a cheesy macroscopic appearance. It is particularly characteristic of the necrotic tissue resulting from tuberculous infection. Microscopically, the architectural outline of the necrotic tissue is completely lost. **Gummatus necrosis** which results from syphilis resembles caseous necrosis microscopically but in the gross has a more rubbery consistency. In **liquefactive necrosis** the dead area softens and eventually liquefies. It is especially characteristic of necrosis in the central nervous system. It may follow other types of necrosis in other tissues, and the term may be applied to the liquefaction of pus in abscesses.

Microscopic recognition of necrosis is aided by nuclear changes in necrotic cells. The nucleus may shrink and stain more intensely basophilic (pyknosis) or may fragment (karyorrhexis). More commonly the nucleus simply loses its ability to stain differentially with basic dyes (karyolysis) so that it fades and eventually is indistinguishable. Necrotic tissues tend to stain diffusely with red acid dyes such as eosin, with lack of any blue or hematoxylin-staining material. Any calcium which precipitates in the necrotic material stains with hematoxylin, thus appearing as bluish masses.

Areas of necrosis act as an irritant to which the adjacent living tissues respond by an inflammatory reaction. Hence, zones of necrosis are surrounded by hyperemia and cellular reaction in the adjacent tissues. Infarcts are described in greater detail on page 114. Zenker's necrosis of voluntary muscle has been described on page 73.

Fat necrosis is most commonly the result of pancreatic disease, which allows release of enzymes which act on fat. The fat of the pancreas, omentum, or other intra-abdominal tissues shows whitish opaque nodules of very characteristic appearance. A zone of congestion and leukocytes surrounds the necrotic areas. Eventually, calcium tends to be deposited in these areas, and a foreign body reaction occurs around them. Fat necrosis may also occur in the breast and other subcutaneous areas, from trauma, toxic agents, circulatory disturbances, and injections. There is necrosis of the fat cells, with release of neutral fat into

tissues and its subsequent change into fatty acids or soaps. An inflammatory reaction occurs, often of foreign-body type with formation of giant cells, and a tumorlike mass may result.

Decubitus is a necrosis and ulceration which develops over bony prominences (e.g., sacrum) in debilitated or emaciated individuals confined to bed for prolonged periods. Pressure and interference with circulation to affected areas seem to be the important factors. Secondary infection commonly occurs in the necrotic areas.

Gangrene

Gangrene is a massive necrosis of tissue, to which there is added an invasion by saphrophytic organisms. Distinction is often made between such infected necrotic tissue (moist gangrene) and an uninfected ischemic necrosis of tissue not surrounded by living tissue (dry gangrene). **Dry gangrene** (or mummification) is a term usually applied to ischemic necrosis of a portion of an extremity, i.e., an infarction of the extremity. The tissue becomes dried out, greenish yellow, and, finally, dark brown or black. Inflammatory reaction in the adjacent living tissue causes a sharp line of demarcation separating healthy and dead tissues. In **moist gangrene**, which may be found in almost any part of the body, saphrophytic organisms invade the dead tissue through wounds or from the respiratory or intestinal tract, causing putrefactive changes. **Gas gangrene** occurs when the invading saprophytes are of the gas-forming group (e.g., the Welch bacillus).

Senile gangrene is a necrosis in an extremity due to interference with blood supply by arteriosclerosis. It is often a dry type, but may be moist and putrefactive. **Diabetic gangrene** is similar, and also due to arteriosclerosis, but tends to occur at an earlier age. Gangrenous extremities due to interference with blood supply may also be due to *Raynaud's disease* (vascular spasm), *ergot poisoning* (vascular spasm), and *thromboangiitis obliterans* (endarteritis).

POSTMORTEM CHANGES

Somatic death, or death of the body as a whole, is followed by some early changes with which it is necessary to be familiar. Somatic

death occurs when respiration and cardiac action cease. Individual cells or tissues may remain alive for variable but short periods of time after somatic death, and some activity may proceed, e.g., mitotic activity going on at the time of death may proceed to complete division of the cells. Very soon, however, irreversible changes occur, such as cooling of the body, development of muscular rigidity, gravitation of blood to dependent parts, clotting of blood, autolysis, and putrefaction. Although varying to some extent with external and internal conditions, these postmortem changes develop with time relationships which may be useful in roughly estimating the time of death for medicolegal purposes.

Cooling of the body (algor mortis) gradually occurs to the temperature of the environment, usually being complete in about forty hours. Occasionally following death from acute infections or certain other conditions, there is increase in temperature of the interior of the body of short duration, due to active metabolism continuing for a short period while the cooling effect of circulation of blood is lacking.

The rate of cooling varies with factors such as environmental temperature, clothing of the body, state of nutrition, etc. It tends to be about 3.5° or 3° F. per hour for the first few hours, gradually decreasing to 1° F. per hour until environmental temperature is reached.

Muscular rigidity (rigor mortis) develops soon after death due to a chemical change in which there is precipitation of protein. It begins first in involuntary muscles, then is noticeable in voluntary muscles about the head and neck, and gradually spreads over the whole body. It usually begins in about four to ten hours, and passes off in three or four days. The time of appearance and the degree of rigor mortis are affected by a number of conditions, so that it is not very reliable as an indication of the exact time of death. Violent exercise, high fever, exhaustion, and high environmental temperature before death tend to hasten development of rigor mortis, while it may be retarded in cachectic individuals or by low temperatures.

Postmortem staining (livor mortis) is due largely to changes in the position and condition of the blood. There develops an irregular reddish discoloration of dependent parts of the body, due to the gravitational sinking of blood. Internal organs, such as the lungs, are affected as well as the skin. Up to ten or twelve hours, the position of the blood, and hence the site of the livor mortis, will change with variation in the position of the body. Hemolysis of red cells occurs with varying rapidity after death, and hemoglobin may lightly stain the aortic lining or serous surfaces. Hemoglobin staining may be hastened in death from infections, particularly if due to hemolytic organisms.

Clotting of blood occurs early after death, and in cases of slow death may actually begin during the agonal period (agonal clots). The postmortem clot is a red, elastic or jellylike clot (eruor clot) which is not adherent to the lining of blood vessels or the heart. In agonal clotting or circumstances in which the clotting is less rapid, a layered clot is formed. When there is

time for gravity to separate the elements of the blood before coagulation is complete, the heavy red cells form a thick layer at the bottom, above which is a grayish layer of leukocytes, and on top a grayish-yellow layer of plasma containing platelets and leukocytes. These layered clots are often found in the heart at autopsy. The deep red portion (cruor clot) is in the dependent part, while the upper part is a tough, elastic, yellowish, translucent mass resembling chicken fat ("chicken-fat clot").

Autolysis is the self-digestion or breakdown of tissues due to ferment produced in the body after death. In some tissues, such as the mucosa of the stomach or gall bladder, autolytic changes are rapid, and good microscopic preparations of such tissues may be difficult to obtain post mortem. In general, the more highly differentiated tissues undergo more rapid autolysis than do supporting or connective tissue structures. Early autolysis results in loss of cellular detail in staining, and may cause some confusion in differentiation from such degenerative processes as cloudy swelling. The cytoplasm of cells tends to become hyaline and granular. Later, staining ability and outline of cells may become indistinct or be lost. Absence of cellular reaction and inflammation helps to distinguish the autolytic changes from antemortem necrosis. Grossly, autolysed organs show softening, and sometimes slight swelling.

Putrefaction in the dead body follows entrance of saprophytic organisms, usually from the intestinal tract. It results in the production of gases (e.g., hydrogen sulfide) and a greenish discoloration of tissues from the reaction of the gases with the iron of tissues and blood. Early greenish discoloration is seen most often in the anterior abdominal wall and in areas of the liver in contact with the bowel. Gas-producing saprophytes growing in viscera may cause a foamy or spongy appearance of the organs, particularly liver. With agonal blood stream distribution of gas-producing organisms, marked degrees of this foamy change in viscera may be encountered on postmortem examination.

References

Atrophy

1. Bradley, H. C.: *Physiol. Rev.* **18**: 173, 1938.
2. Cowdry, E. V.: *Problems of Ageing*, Baltimore, 1942, Williams & Wilkins Co.

Disturbances of Fat Metabolism

3. Miyakawa, G., and Stearns, G.: *J. Bone & Joint Surg.* **24**: 429, 1942 (osteoporosis from steatorrhea).
4. Weinhouse, S.: *Arch. Path.* **35**: 438, 1943 (blood cholesterol).
5. Bell, E. T.: *J. Path. & Bact.* **17**: 147, 1912, **1912**, and **19**: 105, 1914 (staining of fats and lipoids).
6. Connor, C. L.: *Am. J. Path.* **4**: 227 and 235, 1928 (lipochromes).
7. Wells, H. G.: *J. A. M. A.* **114**: 2177 and 2284, 1940.
8. Conn, J. W.: *Physiol. Rev.* **24**: 31, 1944 (obesity, etiologic aspects).
9. Newburgh, L. H.: *Physiol. Rev.* **24**: 18, 1944 (obesity, metabolic aspects).
10. Goldzieher, M. A.: *Am. J. Digest. Dis.* **13**: 40, 1946 (obesity, endocrine aspects).
11. Zeek, P., and Madden, E. M.: *Arch. Path.* **41**: 166, 1946 (sclerema neonatorum).

12. Gurney, R.: *Arch. Int. Med.* **57**: 557, 1936 (obesity, hereditary aspects).
13. Lyon, I. P.: *Arch. Int. Med.* **6**: 29, 1910 (adiposis).
14. Parmelee, A. H.: *J. A. M. A.* **98**: 548, 1932 (lipodystrophy).
15. Goldzieher, M. A.: *Arch. Surg.* **23**: 690, 1931 (lipogranulomatosis).
16. McIntosh, J. F., Waugh, T. R., and Ross, S. G.: *Am. J. Dis. Child.* **55**: 112, 1938 (sclerema neonatorum).
17. Spain, D. M., and Foley, J. M.: *Am. J. Path.* **20**: 783, 1944 (Weber-Christian's disease).
18. Hirsch, E. F.: *Arch. Path.* **25**: 35, 1938 (tissue reactions to fat).
19. Whipple, G. H.: *Bull. Johns Hopkins Hosp.* **18**: 382, 1907 (intestinal lipodystrophy).
20. Jarco, S.: *Bull. Johns Hopkins Hosp.* **59**: 275, 1936 (intestinal lipodystrophy).
21. Reinhart, H. L., and Wilson, S. J.: *Am. J. Path.* **15**: 483, 1939 (intestinal lipodystrophy).
22. Pearse, H. E.: *Surgery* **11**: 906, 1942 (intestinal lipodystrophy).
23. Rosen, M. S., and Rosen, S. H.: *Am. J. Path.* **23**: 443, 1947 (intestinal lipodystrophy).
24. Dible, J. H.: *J. Path. Bact.* **39**: 197, 1934 (fatty degeneration).
25. Dible, J. H., and Gerrard, W. W.: *J. Path. & Bact.* **46**: 77, 1938 (fatty degeneration).
26. Dible, J. H., and Hay, J. D.: *J. Path. & Bact.* **51**: 1, 1940 (fatty degeneration).
27. Simms, H. S., and Stillman, N. P.: *Arch. Path.* **23**: 316, 1937 (fatty degeneration in tissue culture).
28. Best, C. H.: *Science* **94**: 524, 1941 (choline and fatty liver).
29. Dragstedt, L. R.: *J. A. M. A.* **114**: 29, 1940 (lipocaine).
30. Connor, C. L.: *Am. J. Path.* **14**: 347, 1938 (fatty liver).
31. Graham, R. E.: *Bull. Johns Hopkins Hosp.* **74**: 16, 1944 (sudden death with fatty liver).
32. LeCount, E. R., and Singer, H. A.: *Arch. Path.* **1**: 84, 1926 (sudden death with fatty liver).
33. Fuller, R. N.: *Arch. Path.* **32**: 556, 1941 (lipoids in kidney).

Carbohydrate Metabolism

34. Soskin, S.: *Arch. Int. Med.* **71**: 219, 1943 (glycogen).
35. Chipp, H. D., and Duff, G. L.: *Am. J. Path.* **18**: 645, 1942 (glycogen in liver).
36. Von Gierke, E.: *Beitr. z. path. Anat. u. z. allg. Path.* **82**: 497, 1929 (glycogen-storage disease).
37. Van Creveld, S.: *Medicine* **18**: 1, 1939 (glycogen-storage disease).
38. Mason, H. H., and Anderson, D. H.: *Am. J. Dis. Child.* **61**: 795, 1941 (glycogen-storage disease).
39. Crawford, T.: *Quart. J. Med.* **15**: 285, 1946 (glycogen disease).
40. Batchelor, T. M., and Mann, M. E.: *Arch. Path.* **39**: 67, 1945 (glycogenic tumors of heart).
41. Haymond, J. L., and Giordano, A. S.: *Am. J. Clin. Path.* **16**: 651, 1946 (glycogen disease of heart).
42. Ricketts, H. T.: *Proc. Inst. Med. Chicago* **16**: 347, 1947 (hyperglycemia).
43. Lawrence, R. D., Meyer, A., and Nevin, S.: *Quart. J. Med.* **11**: 181, 1942 (hypoglycemia).
44. Moersch, F. P., and Kernohan, J. W.: *Arch. Neurol. & Psychiat.* **39**: 242, 1938 (hypoglycemia).
45. Jones, G. M.: *Am. J. M. Sc.* **213**: 206, 1947 (hypoglycemia).

Cloudy Swelling

46. Davidman, A., and Dolley, D. H.: *J. Med. Res.* **42**: 515, 1921.
47. Lucké, B., and McCutcheon, M.: *Arch. Path.* **2**: 846, 1926, and *J. Gen. Physiol.* **9**: 697, 1926.
48. Smith, J. L., and Rettie, T.: *J. Path. & Bact.* **28**: 627, 1925.
49. Oglivie, R. F.: *J. Path. & Bact.* **35**: 743, 1932.

Hydropic Degeneration

50. Anderson, W. A. D.: South. M. J. **34**: 257, 1941 (sucrose).
 51. Anderson, W. A. D., and Bethea, W. R.: J. A. M. A. **114**: 1983, 1940 (sucrose).
 52. Geiling, E. M. K., and Cannon, P. R.: J. A. M. A. **111**: 919, 1938 (diethylene glycol).
 52a. Kulka, J. F., Pearson, C. M., and Robbins, S. L.: Am. J. Path. **26**: 349, 1950 (vacuolar nephropathy).
 53. Lucké, B., and McCutcheon, M.: Arch. Path. **10**: 662, 1930 (effect of injury on cellular permeability to water).

Hyaline Droplet Degeneration

54. Smetana, H., and Johnson, F. R.: Am. J. Path. **18**: 1029, 1942 (kidney).
 55. Crooke, A. C.: J. Path. & Bact. **41**: 339, 1935 (pituitary).

Zenker's Degeneration

56. Wells, H. G.: Arch. Path. **4**: 681, 1927.
 57. Forbus, W. D.: Arch. Path. **2**: 316, 1926.

Amyloid

58. Hass, G. M., et al.: Arch. Path. **30**: 240, 1940; **34**: 92, 1942; and **35**: 226, 1943.
 59. King, L. S.: Am. J. Path. **24**: 1095, 1948.
 60. Stemmerman, M. G., and Auerbach, O.: Am. J. M. Sc. **208**: 305, 1944.
 61. Lindsay, S., and Kuorp, W. F.: Arch. Path. **39**: 315, 1945.
 62. Taran, A., and Eckstein, A.: Am. J. M. Sc. **203**: 246, 1942 (congo red test).
 63. Lipstein, S.: Am. J. M. Sc. **195**: 205, 1938 (congo red test).
 64. Bauer, W. H., and Kuzma, J. F.: Am. J. Clin. Path. **19**: 1097, 1949 (paramyloid).
 65. Pearson, B., et al.: Arch. Path. **32**: 1, 1941 (primary systemic).
 66. Eisen, H. N.: Am. J. Med. **1**: 144, 1946 (primary systemic).
 67. Butt, E. M.: Arch. Path. **10**: 859, 1930 (experimental).
 68. Ku, D. V., and Simon, M. A.: Arch. Path. **18**: 245, 1934 (experimental).
 69. Dick, G. F., and Leiter, L.: Am. J. Path. **17**: 741, 1941 (experimental).
 70. Smetana, H.: J. Exper. Med. **45**: 619, 1927 (relation to reticulo-endothelial system).
 71. Tarr, L., and Ferris, H. W.: Arch. Int. Med. **64**: 820, 1939 (with multiple myeloma).
 72. Baber, M. D.: Lancet **1**: 210, 1947 (macroglossia).
 73. Barnard, W. G., et al.: J. Path. & Bact. **47**: 311, 1938 (macroglossia).
 74. Abramowitz, E. W., and Isaak, L.: Arch. Dermat. **40**: 13, 1939 (cutaneous amyloidosis).
 75. Bell, E. T.: Am. J. Path. **9**: 185, 1933 (renal amyloidosis).
 76. Warren, S.: Am. J. Path. **6**: 161, 1930 (amyloidosis of muscle).
 77. Snapper, I., et al.: Chinese M. J. **57**: 201, 1940 (amyloidosis of adrenals).
 78. Tiber, A. M., et al.: Arch. Int. Med. **68**: 309, 1941 (hepatic function with amyloidosis).
 79. Lindsay, S.: Am. Heart J. **32**: 419, 1946 (heart).

Pathologic Calcification

80. Barr, D. P.: Physiol. Rev. **12**: 593, 1932.
 81. Wells, H. G.: Arch. Int. Med. **7**: 721, 1911.
 82. Anderson, W. A. D.: Arch. Path. **27**: 753, 1939; J. Pediat. **14**: 375, 1939; and J. Urol. **44**: 29, 1940.
 83. Mulligan, R. M.: Arch. Path. **43**: 177, 1947 (metastatic).
 84. Meeker, D. R., and Kesten, H. D.: J. Biol. Chem. **113**: 289, 1936 (chemistry).

85. Ham, A. W.: Arch. Path. **14**: 613, 1932 (hypervitaminosis D).
 86. Gomori, G.: Am. J. Path. **19**: 197, 1943 (phosphatase).
 87. Lutz, J. F.: Ann. Int. Med. **14**: 1270, 1941 (calcinosis).
 88. Rosenberg, E. F.: J. A. M. A. **115**: 1791, 1940 (calcinosis).
 89. Rothstein, J. L., and Welt, S.: Am. J. Dis. Child. **52**: 368, 1936 (calcinosis).

Gout

- 89a. Adlersberg, D.: Bull. New York Acad. Med. **25**: 651, 1949.

Pigmentations

90. Jeghers, H.: New England J. Med. **231**: 88, 122, and 181, 1944 (skin pigmentation).
 91. Bloch, B.: Am. J. M. Sc. **177**: 609, 1929 (melanin).
 92. Laidlaw, G. F.: Am. J. Path. **8**: 477, 1932 (melanin).
 93. Percival, G. H., and Stewart, C. P.: Edinburgh M. J. **37**: 497, 1930 (melanin).
 94. McMichael, J.: J. Path. & Bact. **39**: 481, 1931, and Edinburgh M. J. **42**: 97, 1935 (hemosiderin in spleen).
 95. Muir, R., and Niven, J. S. F.: J. Path. & Bact. **41**: 183, 1935 (hemosiderin).
 96. Sheldon, J. H.: Haemochromatosis, Oxford University Press, 1935.
 97. Wyatt, J. P., Mighton, H. K., and Moragues, V.: Am. J. Path. **26**: 883, 1950 (transfusional siderosis).
 97a. Schwartz, S. O., and Blumenthal, S. A.: Blood **3**: 617, 1948 (exogenous hemochromatosis).
 97b. Krainin, P., and Kahn, S. S.: Ann. Int. Med. **33**: 453, 1950 (hemochromatosis).
 97c. Granick, S.: Bull. New York Acad. Med. **25**: 403, 1949 (iron metabolism).
 98. Fairley, N. H.: Brit. M. J. **2**: 213, 1940 (methemalbumin).
 99. Morrison, D. B., and Anderson, W. A. D.: Pub. Health Rep. **57**: 90 and 161, 1942 (malarial pigment).
 100. Coolidge, T. B.: J. Biol. Chem. **132**: 119, 1940 (van den Bergh reaction).
 101. Watson, C. J.: Blood **1**: 99, 1946 (hemoglobin derivatives).
 102. Watson, C. J.: New England J. Med. **227**: 663 and 705, 1942 (bile pigments).
 103. McNeely, J. W.: Quart. J. Med. **16**: 390, 1923 (jaundice).
 104. Rich, A. R.: Bull. Johns Hopkins Hosp. **47**: 338, 1930 (jaundice).
 105. Chandler, F. G., et al.: Brit. M. J. **2**: 1173, 1939 (porphyrinuria).
 105a. Marietta, J. S.: South. M. J. **42**: 958, 1949 (porphyria).
 105b. Dunsky, I., Freeman, S., and Gibson, S.: Am. J. Dis. Child. **47**: 305, 1947 (porphyria).
 106. Humble, J. G.: Quart. J. Med. **15**: 299, 1946 (chloroma).
 107. Garrod, A. E.: Inborn Errors of Metabolism, ed. 2, London, Frowde, Hodder and Stoughton, 1923.
 108. Mason, V. R., Courville, C., and Ziskind, E.: Medicine **12**: 355, 1933 (porphyrinuria).
 109. Popper, H., Gyorgy, P., and Goldblatt, H.: Arch. Path. **37**: 161, 1944 (ceroid).
 110. Pappenheimer, A. M., and Victor, J.: Am. J. Path. **22**: 395, 1946 (ceroid).
 111. Olcott, C. T.: Am. J. Path. **24**: 813, 1948 (argyria).
 112. Rukstina, G. J.: Arch. Path. **31**: 640, 1941 (tattoos).
 112a. Smith, B. F.: J. A. M. A. **144**: 1074, 1950 (tattooing and hepatitis).
 113. Miner, R. W., ed.: The Biology of Melanomas, Spec. Pub. of the New York Academy of Sciences, Vol. 4, 1948.

Chapter 5

DISTURBANCES OF CIRCULATION

VIRGIL H. MOON

ABNORMAL DISTRIBUTION OF FLUIDS

Circulatory disturbances arising from cardiac and vascular abnormalities are discussed in Chapters 19 and 20. The normal volume and distribution of body fluids, and the physiologic principles which apply to fluid environment are set forth in Chapter 2. Other factors in the distribution of fluids are considered here.

The circulatory system accomplishes the transportation and distribution of all substances used or produced by the cells, including oxygen, carbon dioxide, salts, water, nutritional substances, metabolites, hormones, waste products, and heat. The transportation and gross distribution of these are performed by the heart and large vessels. The distribution to the ultimate consumers, the cells, and the collection of metabolites and waste products from them are accomplished by the endothelium of the blood and lymph capillaries. Endothelium is a highly specialized tissue adapted to the functions of collection and distribution. It plays the chief role in the elimination of water, heat, and waste products in the excretory organs, and its special qualities are indispensable in the maintenance of fluid balance. These functions depend upon filtration and diffusion through a membrane as thin and delicate as the wall of a soap bubble.

Fluid Balance

This term applies to the mechanisms which control the volume and distribution of fluids in the animal organism. Many factors are involved, hence the mechanism of fluid balance is complex. The normal volume and electrolytic content of the blood are maintained chiefly by renal function. An excess of fluid is excreted promptly by the kidneys and by perspiration; a part may be stored as tissue fluid. If saline solution is given intravenously,

both the salts and the water are eliminated rapidly by the kidneys, thus maintaining the blood volume and the concentration of electrolytes within physiologic limits.⁴

Renal tubular functions are governed largely by the pituitary and the adrenal cortex.^{3, 5} These functions include the excretion of water and K and the retention of Na when it is not in excess. Deficiency of corticoid hormones results in wastage of sodium chloride and carbonate and retention of K. An excess of DCA will cause retention of Na accompanied by retention of water. Variations in the concentration of Na and other electrolytes cause variations in osmotic pressure which in turn affect the distribution of fluids. One pituitary hormone, ACTH, stimulates the adrenal to increased production of corticoid hormones with ensuing variations in the distribution of water and electrolytes.

The pituitary and adrenal cortex exert also extrarenal influences on water distribution, which complicate further the mechanism of fluid balance. Some of the observed effects under different physiologic conditions seem paradoxical. Workers in this field freely admit the present incompleteness of their evidence. The functions of these glands may be disturbed by various pathologic conditions, thereby disturbing the movement and the distribution of water and of electrolytes.

One function of the adrenal cortical hormones is to control the permeability of cell walls and membranes. This directly affects the capillary endothelium which plays a major role in the movement of fluid between the blood and the tissue spaces. Normally the capillary membrane permits water, certain gases, and crystalloids in solution to pass freely in either direction, but it is relatively impervious to colloids—the proteins of the plasma. Hence the plasma has a higher protein content than the tissue fluid or lymph. The pressure of blood within the capillaries tends to force fluid out of the blood into the tissue spaces. This tendency is countered by the osmotic pressure of the plasma colloids, which tends to draw fluid into the blood.

Normally the blood is maintained at a fairly constant volume; conditions tending to raise or lower its volume are promptly countered by forces tending to return it to the normal level. Loss of blood reduces the capillary blood pressure, whereupon the osmotic attraction of the plasma colloids draws fluid from the tissues into the blood. This process rapidly restores the blood volume after hemorrhage. An excess

of fluid in the blood is promptly reduced by the escape of fluid into the tissues or by the excretory channels. These functions are mediated by the endothelium.

It is apparent that fluid balance depends largely upon normal qualities of the capillary endothelium; it plays the essential part of a diffusion membrane in osmotic processes. When this membrane becomes abnormally permeable, osmotic processes through it are interrupted. This disturbs the distribution of fluids and results in edema. Capillary walls so permeable that they allow the plasma to pass freely into the tissue spaces are incapable of maintaining fluid balance.

Dehydration.¹—This is a disturbance of fluid balance in which the output of water exceeds the intake, causing a reduction of the body water below the normal level. This may result from insufficient intake of water, excessively high external temperature, or prolonged fever. Psychotic patients may refuse to drink. Acute diarrhea, persistent vomiting or diuresis may cause excessive loss of water. Asiatic cholera produces rapid dehydration which may be fatal. The mortality from this disease was reduced 50 per cent by repeated intravenous infusions of saline solution.⁶ Severe loss of water may result from disturbance of acid-base equilibrium from sundry causes including conditions which reduce the total quantity of electrolytes in the body fluids. Occasional instances of dehydration are of hormonal origin, e.g., Simmonds' disease.

Results of dehydration include loss of weight, the skin becomes loose, wrinkled and the eyeballs sunken, disturbances of the acid-base balance toward the acid side, anhydremia, decreased circulation and oxidation, lowered renal excretion, retention of nitrogenous wastes, reduced cardiac output, rapid pulse, profound weakness, and collapse.

Edema

Edema is defined as an abnormal accumulation of fluid in the cells, tissue spaces, or cavities of the body. It is caused by conditions which interfere with the normal movement of blood, tissue fluid and lymph, or which disturb the mechanism of fluid balance. These include *obstruction to the flow of lymph*, *abnormal permeability of capillary endothelium*, *increased capillary blood pressure*, *decreased plasma colloidal osmotic pressure*, *decreased extravascular tissue pressure*, and functional abnormalities of the kidneys, adrenal cortex, and pituitary.

LYMPH AND TISSUE FLUID

Fluids derived from the plasma of the blood and from the metabolic activity of cells constitute the tissue fluid from which lymph is derived. The watery portion of this and its content of diffusible sub-

stances may be resorbed into the blood through the capillary walls. The remainder, including colloids, seeps into the lymphatic capillaries. The volume of lymph flowing from an area is increased by massage or passive motion, physiologic activity of the tissue, an increase in the venous pressure, and permeability of the capillary endothelium. These conditions may not cause edema so long as the outflow of lymph from the area is adequate to remove the fluid.⁸

Lymphedema is the term applied to an increase of tissue fluid resulting from obstruction to the flow of lymph from an area. Instances of this are seen after complete surgical removal of the axillary lymph nodes; this leads to diffuse edema of the arm. Likewise, obstruction of the inguinal lymphatics, as by filaria, may cause chronic edema of the scrotum and of the legs—*elephantiasis*. Obstruction of the main abdominal or thoracic lymphatic channels may be caused by tumors, filaria, or by chronic inflammation of the lymph nodes. This may produce edema of the tissues drained by those lymph channels. Occasionally, large accumulations of fluid in the pleural or peritoneal cavities result; the latter is called *chylous ascites*.

INCREASED ENDOTHELIAL PERMEABILITY

The most frequent cause of edema is increased capillary permeability. It has been shown¹² that any agent or condition injurious to endothelium increases its permeability to plasma colloids. This effect deranges also the mechanisms of fluid balance and of absorption. These processes require the presence of a normal semipermeable membrane—the endothelium—for their operation. Increased permeability of capillary walls, from whatsoever cause, allows transudation of plasma into the tissue spaces, leading to edema unless the lymph drainage is adequate to remove the fluid.

Heidenhain¹⁰ noted that peptone, extracts of liver, pancreas, and other tissues, and extracts of various marine animals would cause an increased flow of lymph if given intravenously to dogs. He believed this effect was due to increased secretory activity of endothelium. Starling¹⁵ showed that these "lymphagogues" were in fact capillary poisons; that their effects resulted from increased endothelial permeability. Many other substances have been shown to produce the same effects.^{11, 12} These include cer-

tain alkaloids, toxins and other products of bacterial growth, foreign proteins and protein split products, histamine, bile and cholic salts, venoms of reptiles and insects, many drugs, chemicals, and poisons. Such agents have one property in common—that of damaging endothelium and increasing its permeability to blood plasma.

Edema due to abnormal permeability of endothelium may be produced experimentally by injections of capillary poisons, or of proteins to which the animal is sensitive, or by reducing the oxygen supply to a tissue. If the agent used affects a limited area of tissue, as the bite or sting of an insect, the edema will be local. If the effect is systemic, it is seen particularly in mucosae, in soft visceral tissues, and in the meninges. The edema fluid has a high content of proteins, and it may contain erythrocytes.

This type of edema occurs in a wide variety of clinical conditions, among which may be mentioned *severe infections* such as influenza, meningitis, septicemia, typhoid, diphtheria, and others, *metabolic intoxications* such as eclampsia, *icterus gravis*, and diabetes, *anaphylactic reactions*, "hay fever," transfusions with incompatible blood, *abdominal emergencies* such as visceral perforation, pancreatitis, peritonitis, and intestinal obstruction, *asphyxia* from any cause including the inhalation of carbon monoxide and other fumes, *poisoning* with various drugs and chemicals, and overdoses of sedatives. This type of visceral edema is seen also after severe traumatic injuries, burns, and after death by *secondary shock* (*q.v.*) from other causes. The generalized edema which may accompany the acute stage of glomerulonephritis is attributed to capillary permeability. Systemic edema (*anasarca*) is usually accompanied by effusions of fluid into the serous cavities.

Inflammatory Edema.—Inflammatory edema is an instance of local edema resulting from increased permeability of endothelium. Wheals, urticaria, the bites or stings of insects, burns, infections, and the application of irritating drugs or chemicals are examples. Blisters or blebs, sometimes called bullae, frequently result from local cutaneous edema. In this instance the pressure of the fluid causes a separation of the superficial layer of epithelium; the space is filled with fluid.

Inflammatory edema has a high content of the plasma proteins including fibrinogen if endothelial permeability is

greatly increased. The fluid contains leukocytes as discussed under *Inflammation*, page 16.

Physiologists^{9, 11, 13} have shown that injury to tissue cells causes the release of cytoplasmic substance which causes dilatation and increased permeability of the adjacent capillaries. The "triple response" described by Lewis, caused by any type of mild local injury, includes arteriolar dilatation, hyperemia of the capillaries and venules, and edema (the wheal) resulting from transudation of plasma into the tissue spaces. He attributed these effects to a specific substance which he called "H substance" because its effects resembled those of histamine. Others believe that no specific substance is concerned, that the effects are produced by cytoplasmic substance released from the damaged cells. This reaction is the initial phase of inflammation (see page 15).

Allergic Edema.—Local edema often results from allergic reactions. The swelling of nasal mucosa which accompanies "hay fever" is an example. Edema of the lungs may result from the inhalation of dust to which the person is sensitive. Local anaphylactic reactions, produced by injecting protein into the skin or other tissues of a sensitized subject, is another instance. Systemic anaphylaxis is accompanied by edema, analogous to urticaria which is a local reaction of the same kind. In each of these instances endothelial permeability is the mechanism involved.

Angioneurotic Edema.—The rapid development of edema without apparent cause has been assigned to disturbances of neurogenic origin. This usually is local, affecting a limb, the cervical region, or the respiratory tract as the pharynx, glottis, and/or the lungs. It is known that the tonus of capillaries is influenced by nerve agencies and that disorders of these may affect the state of the endothelium, causing local edema by increased endothelial permeability. An instance of this may be produced experimentally by cutting both vagus nerves low in the neck. Pulmonary edema develops rapidly, even when the animals are not allowed food or drink, which might enter the respiratory passages due to disturbances of the mechanism for swallowing. In such experiments the blood becomes concentrated and the edema fluid has a chemical composition like that of plasma, indicating that capillary permeability is the mechanism by which the edema originated. Some instances of edema, classed as angioneurotic, probably are allergic in origin.

DECREASE IN PLASMA PROTEINS

Decrease in plasma proteins causes edema by deranging the equilibrium between the forces concerned in water balance. The osmotic attraction of the plasma colloids for water depends largely upon the albumin content. When this has been reduced to 3 Gm. per 100 ml. or lower, the colloid osmotic pressure is no longer sufficient to counteract the hydro-

static pressure of the blood, which tends to drive fluids out of the blood into the tissue spaces. This causes progressive accumulation of extravascular fluid.

Nephrotic Edema.—The subacute stage of nephritis is characterized by marked albuminuria. If this continues, it may lower the albumin content seriously, causing a reversal of the albumin-globulin ratio and systemic edema. Albumin has smaller molecules than globulin, and is the major factor in osmotic processes. When the content of albumin falls below the physiologic level, transudation of fluid into the tissue spaces results in edema. The fluid accumulates both in visceral and in somatic tissues; it has a low content of protein, in which particular it differs from that of acute nephritis or of edema caused by increased capillary permeability.

Nutritional or Famine Edema.—After prolonged undernourishment, as during famine or incident to metabolic or nutritional disorders, the plasma proteins may be seriously depleted. The reduced osmotic pressure of the plasma allows the movement of fluid from the blood into the tissues.

INCREASE IN VENOUS PRESSURE

An abnormally high venous blood pressure raises the hydrostatic pressure within the capillaries. If this pressure more than counterbalances the osmotic attraction of the plasma colloids for water, fluid may accumulate in the tissues involved. Several instances of edema are produced by this mechanism.

Postural edema may result from standing motionless in one position. This develops in the subcutaneous tissues of the feet and ankles. Postural edema is not so likely to form when the person is active as in walking, for, while the venous pressure due to gravity is equally high, the action of the muscles facilitates the escape of the tissue fluid via the lymphatics. This type of edema usually is transient and disappears after rest in a horizontal position.

Passive congestion due to mechanical obstruction of the veins causes an increase in the venous blood pressure and tends to cause edema by the mechanism described. Instances of this are seen when thrombosis (*q.v.*) of veins has oc-

curred, especially when large vessels, as the common iliac vein, are obstructed. The pressure of a tumor or of a pregnant uterus upon the iliac vein may cause edema of the leg.

Portal cirrhosis usually causes obstruction to the portal circulation within the liver. This impedes the outflow of blood from the abdominal organs and causes an increased capillary blood pressure in all the tissues drained by the portal vein. This produces a transudation of fluid, called *ascites*, in the peritoneal cavity. Large quantities of ascitic fluid are drained surgically from the abdomen for mechanical relief in the late stages of cirrhosis.

Cardiac edema results from circulatory deficiency and passive congestion, incident to ineffective cardiac function. It may be prominent during life when some valvular or other defect is not adequately compensated and it is found regularly at necropsy after congestive heart failure. Cardiac edema tends to be systemic in distribution but is most marked in the lungs and in dependent parts of the body. It involves subcutaneous tissues as well as viscera, and causes effusions in serous cavities. The fluid has a high protein content.

Increased capillary blood pressure is not the sole cause for edema in the instances described. In each of them the circulation is impaired and the oxygen supply to the tissues is subnormal. Lack of oxygen increases the permeability of endothelium; hence the edema results from a combination of increased hydrostatic pressure and increased permeability of capillary walls.

DECREASED EXTERNAL PRESSURE

This condition tends to increase the extravascular fluid by the same mechanism as an increased capillary blood pressure, but instances of its effect are not so common. A vacuum cup applied to a skin surface for a few minutes will cause local cutaneous and subcutaneous edema. This disappears rapidly when normal atmospheric pressure is restored. Aviators flying at high altitude often develop grave circulatory disturbances even though supplied abundantly with oxygen. The same phenomena occurred during tests in low-pressure chambers. When death resulted, marked edema and hyperemia of the viscera were among the conditions found.¹⁴ Apparently, decreased barometric pressure disturbs the distribution of blood and fluid in such instances.

CONGENITAL EDEMA (MILROY'S DISEASE)

This is a chronic mild form of edema which may be present soon after birth or may develop later. It is thought to be congenital but otherwise its etiology is not known. It affects particularly the lower limbs and may be due to some congenital defect of the lymphatic drainage.

MORPHOLOGIC AND FUNCTIONAL EFFECTS OF EDEMA

All tissues of the body excepting bone, hair, and nails may be involved, but edema is most marked in the soft tissues such as the lungs, mucosae, glandular structures, and areolar connective tissue. Slight subcutaneous edema is seen first in soft parts, as about the eyes and the external genitalia. The area is swollen, doughy in consistence, and inelastic so that it "pits," i.e., an imprint remains after temporary pressure made by the fingers. Edematous tissue is translucent and pale in color unless congestion is also present. It appears gelatinous when incised, and fluid oozes or flows from the cut. The fluid may be clear, yellowish, or pink in color. On histologic examination the collagenous fibers may be swollen by absorbed fluid. The most significant feature is the presence of faintly acidophilic material in the intercellular spaces. This represents the protein content of the fluid, coagulated by the fixative. This coagulation may cause the formation of minute granules or the protein may remain optically homogeneous (Figs. 76 and 83).

Emphasis has been laid upon variations in the density of the edema fluid: that having a specific gravity of 1.018 or more was called "exudate," and fluid having a specific gravity of 1.015 or less was called "transudate." Such a distinction is both hypothetical and impractical, serving no useful purpose. Edema fluid resulting from impoverished plasma colloids, as in nephrosis or nutritional edema, is watery and contains less protein than that resulting from abnormal endothelial permeability. But the degree of permeability affects the amount of plasma protein which escapes with the fluid and this varies between wide limits. In acute inflammatory edema the fluid is practically whole plasma; thus in blebs or blisters, formerly called "transudates," the specific gravity of the fluid is usually

above 1.018. Determination of the specific gravity of the fluid seldom is useful in determining the cause of the edema either clinically or at necropsy.

Local edema results from causes affecting a limited area, while in general edema the cause affects the body as a whole. The latter is called *anasarca*. An excess of fluid in the pleural or pericardial sacs is called *hydrothorax* or *hydropericardium*, respectively. Fluid in the peritoneal cavity is called *ascites* or *hydroperitoneum*; that in the tunica vaginalis, *hydrocele*. Obstruction to the escape of cerebrospinal fluid may cause enormous distention of the cerebral ventricles and pressure atrophy of the brain. This is called *hydrocephalus*.

Pathologic Physiology.—Edema is a condition secondary to other disorders. Often the primary condition itself is of greater importance than the edema. The accumulation of fluid locally may disturb physiologic functions; fluid in the pericardial or pleural cavities may embarrass cardiac or respiratory movements; ascites may so distend the abdomen as to make breathing difficult. Cerebral edema leads to increased intracranial pressure and causes disturbances of cerebral functions. Edema of the pharynx and glottis may threaten to cause suffocation. The rapid accumulation of fluid in the alveoli of the lungs may literally drown the patient.

Edema contributes to infection; the albuminous fluid is an excellent culture medium, and the impaired circulation lowers the resistance to infection. If bacteria gain entrance to the fluid in the body cavities, pleuritis or peritonitis will develop. Almost half of those having nephrotic anasarca die of intercurrent infection. Those having edema of the lungs from passive congestion may develop a terminal or secondary pneumonia, often called *hypostatic*. The same result may follow pulmonary edema from other causes. A majority of patients in whom a sublethal degree of shock persists for a few days develop pneumonia by this mechanism.¹⁴

Edema of long duration, particularly in subcutaneous tissues, leads to proliferation of fibrous tissue. This causes brawny induration, thickening, and inelasticity. *Myxedema*, caused by hypothyroidism, is discussed in Chapter 36.

HEMORRHAGE

The term *hemorrhage* denotes escape of blood from within the vascular system. It may result from trauma, from excessive blood pressure, or from some disease which weakens the vascular or cardiac walls.

The sudden loss of a considerable volume of blood brings compensatory

mechanisms into play immediately. Serious hemorrhage causes prompt decline in blood pressure which diminishes further loss. The clotting mechanism is accelerated; the coagulability of the blood is increased within ten minutes after hemorrhage.^{17, 18} There is retraction and contraction of the medial coat of injured artery walls and the endothelial linings become curled up and crenated. These changes facilitate clot formation and mechanical plugging of the injured vessel. An underfilled state of the vessels, as from hemorrhage or shock, activates the carotid sinus reflex. This causes generalized vasoconstriction, reducing the volume capacity of the vascular bed and the volume flow of blood.

hours.²⁵ The plasma will regain its normal content of protein within a few hours, but the regeneration of erythrocytes is much slower, requiring days or weeks.

The carotid sinus reflex also activates the adrenal medulla to discharge adrenaline—the “alarm reaction”²⁶—which stimulates the heart and causes arterial contraction, thus counteracting the blood pressure. Adrenalin also mobilizes glucose from the liver and causes the spleen to contract and to discharge its reserve of red blood cells into the circulation.

The depletion of body fluids causes thirst. There is moderate oliguria proportionate to the severity of the hemorrhage. If this has reduced the blood pressure to about 70 mm. Hg, no urine is secreted.²⁴ However, this is transient and normal renal function is resumed when the blood volume and pressure are restored to a physiologic level. Blood chemical

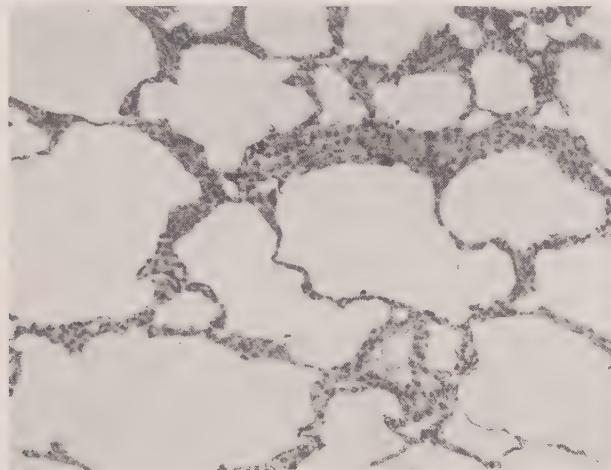


Fig. 74.—Photomicrograph showing ischemia of lung, the result of successive bleedings, ending fatally in thirty-one hours.

This vasoconstriction affects not only the arteries but the precapillaries and capillaries. It causes pallor of the skin and mucosae, a decrease in the peripheral temperature, in the pulse pressure, and the capillary blood pressure. The latter leads to an immediate shift of fluid from the tissues into the plasma, tending to restore the blood volume but decreasing its content of erythrocytes. When blood is withdrawn slowly by syringe from an animal, the last portion is more dilute than the first, indicating that the fluid shift began while the hemorrhage was proceeding.¹⁷ After a loss of 500 ml. by a healthy person, the blood volume will be restored usually within twenty-four

alterations include a decreased alkaline reserve and increased blood sugar.

A plausible explanation for the vascular phenomena is that renal ischemia, due to decreased arterial pressure, causes the release of VEM^{37, 55} which causes arteriolar contraction in systemic areas, thus decreasing the volume capacity of the vascular bed and diminishing the volume flow of blood. Goormaghtigh's²² work indicates that secretory cells in the walls of preglomerular arterioles (the juxtaglomerular apparatus) discharge a powerful vasoconstrictive substance. Perhaps this is related to VEM and to renin described by Goldblatt²¹ and others. The origin of renin has not been shown but an increased concentration of it has been found in animals after hemorrhage, in secondary shock, and in other conditions of hypotension. The effects of renin on the circulation result from renal ischemia and hence are more delayed than those of the carotid sinus reflex.

The belief that hemorrhage causes an increased pulse rate apparently was not based on controlled observations. A number of workers^{20-27, 28} have reported studies on human volunteers

the rule." The changes in blood pressure were negligible until syncope was approaching. Restoration of blood volume to normal required from three to ninety hours, except when trans-



Fig. 75.—Lung of dog after death from secondary shock of thirty-six hours' duration. Capilliovenous hyperemia is seen grossly. (From Moon, V. H., Shock: Its Dynamics, Occurrence and Management, Philadelphia, 1942, Lea & Febiger, p. 124.)

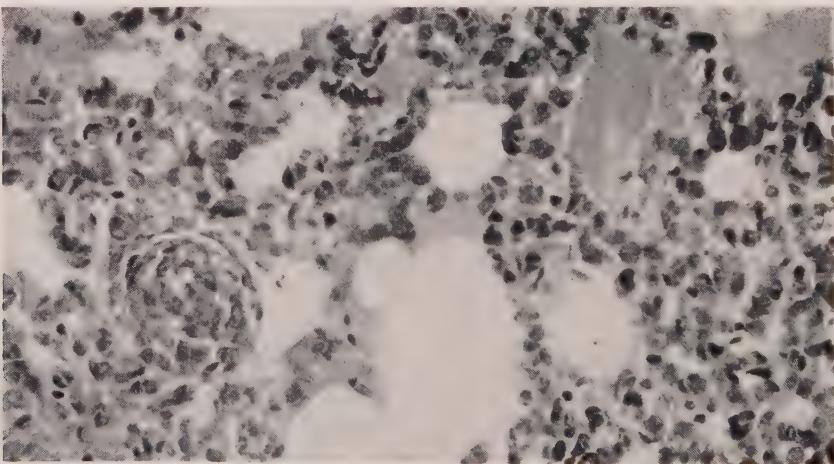


Fig. 76.—Photomicrograph of lung shown in Fig. 75. Edema and capilliovenous hyperemia are shown.

after hemorrhages ranging from 500 to 1,115 ml. Ebert's subjects lost from 15 to 20 per cent of their total blood volume in six to thirteen minutes; in these the pulse rate ranged from 36 to 40 per minute; other reports were in agreement with this. "During the period of severe symptoms, profound bradycardia is

fusions were given. Neither the blood chlorides nor urea showed significant changes. Some of the subjects were nauseated but no vomiting was recorded.

Causes for Hemorrhage.—The effects of rupture of vessels incident to wounds

or other trauma are obvious. The causes for spontaneous hemorrhage are numerous and include types of disease such as aneurysm, arteriosclerosis, and local infections which may weaken the vascular walls. Necrosis of tissue may erode the walls, as in ulcers of the alimentary tract and in pulmonary tuberculosis. Systemic diseases such as purpura, leukemia, and scorbustus are accompanied by hemorrhage in and beneath mucous, serous, and cutaneous surfaces. The same may occur incident to infections of unusual severity, as plague or smallpox. After death by poisoning, as by mercurials, arsenicals, phosphorus, and others, ecchymoses are found in mucous and serous surfaces. Similar effects may be produced by bacterial and other toxins. Anoxia may cause petechiae and ecchymoses. These are seen characteristically after poisoning with cyanides, with CO, and after death by asphyxia or anoxia from any cause.

A number of terms are used to denote hemorrhages under varying conditions. *Hematoma* is a local mass of blood, usually clotted, within some tissue. *Ecchymoses* and *petechiae* imply small hemorrhages resulting from the dissolution of the walls of capillaries and venules. *Hematocele* is hemorrhage into the tunica vaginalis. *Epistaxis* is hemorrhage from the nose. *Hemoptysis* is the coughing up of blood from hemorrhage in the lungs or bronchi. *Hematemesis* is the vomiting of blood. *Melena* is the presence of dark, partly decomposed blood in the stools. *Hematuria* is blood in the urine. *Hemothorax*, *hemopericardium*, and *hemoperitoneum* refer to hemorrhages in those cavities respectively.

Purpura is the term applied to spontaneous hemorrhages into various tissues, as skin, mucosae, joints, and others. This is a sign of some disease affecting the blood-vascular system rather than a disease in itself. The *immediate* cause in each instance is degeneration or fragility of the capillaries. It is held that the platelets are essential to the maintenance of capillary integrity. The endothelial cells are held together by a cement substance⁷; when this is weakened by "wear and tear" or other cause, it becomes sticky and platelets adhere to it thereby helping to maintain its continuity. In the absence of platelets, capillary fragility

develops. Hence two groups of conditions may operate to cause purpuric hemorrhages: (1) those which cause deficiency of platelets, and (2) those which affect endothelium, causing capillary walls to disintegrate.

(1) Primary *thrombocytopenic purpura* is a disease entity whose etiology is not clearly established. It has not been proved whether the low platelet count results from deficient formation of platelets or from their destruction by the spleen or by a platelet antibody of splenic origin.⁷⁵ Splenectomy has afforded relief in many cases but not in all.

This condition, known also as *purpura hemorrhagica* (Werlhof's disease) manifests itself by hemorrhages in the skin, respiratory, gastrointestinal, and genitourinary mucosae, often in the meninges, brain, and elsewhere. There is great variation in the severity and clinical course. In some, the attacks are mild and intermittent; in others, severe hemorrhages cause death in a few days. The disease occurs more frequently in women than in men, and between the ages of 12 and 45 years. Capillary fragility is demonstrable as a clinical sign. The spleen is moderately enlarged, weighing 200 to 400 grams. The bone marrow shows no characteristic abnormality (see also page 904).

Secondary *thrombocytopenia* is a low platelet count which may result from defective formation of platelets by the bone marrow, as in leukemia, aplastic anemia, chronic poisoning with chemicals such as benzol which inhibit the blood-forming function, and chronic infections. Atomic radiation may interrupt blood formation completely, resulting in extensive purpuric hemorrhages. Possibly this agent also damages endothelium.

(2) Various drugs, as arsenicals, sulfonamides, iodides, and others, may cause capillary hemorrhage by direct toxic effects on endothelium. The same is true of allergic reactions and transfusions with incompatible bloods. Snake venoms, particularly those of the pit vipers, contain enzymes which cause dissolution of endothelium with widespread diffuse hemorrhages as a result. Fulminating infections, such as typhus, smallpox, meningitis, staphylococcus or streptococcus bacteremia, diphtheria, and others, cause hemorrhages by their toxic effects upon endothelium.

Lack of vitamin C, as in scurvy, causes deterioration of capillary walls with resulting hemorrhages in mucous surfaces.

Vitamin K is essential to the normal production of prothrombin (see page 418) by the liver. Deficiency of it results in loss of blood by spontaneous hemorrhages in the gastrointestinal mucosae and elsewhere. This is seen in hemorrhagic disease of the newborn and in certain hepatic diseases. Vitamin K is found in alfalfa, in spinach, and in other green vegetables. Also it is produced by the action of bacteria normally present in the intestines. It is stored in the liver; hence hepatic damage reduces this function. Also in the absence of bile in the intestinal tract, vitamin K is not

absorbed; hence delayed clotting and spontaneous hemorrhages often accompany obstructive jaundice.

Sequelae.—Hemorrhage into the gastrointestinal tract or the abdominal cavity has the same systemic effects as external hemorrhage. In some instances the mass of extravasated blood produces mechanical effects. In cerebral hemorrhage the blood infiltrates the adjacent brain substance and destroys or impairs its function. Also, the total volume of the brain is increased proportionally to the amount of the hemorrhage. Since the skull forms a rigid container, the increased volume raises the intracranial pressure. Hemorrhage into a pleural cavity will reduce the volume of that lung; in the pericardial cavity, the mass of blood may so hinder the filling of the ventricles during diastole that death by cardiac tamponade results.

Morphologic Effects.—Severe or fatal hemorrhages produce a characteristic state of ischemia in all the organs. The lungs, liver, kidney, muscles, and the mucous and serous surfaces are pale. (Fig. 74.) The organ weight is reduced and the tissues are drier than normal. Unless some accompanying condition has operated to produce capillary atony or endothelial permeability, there will be no edema nor petechiae.

Internal nonfatal hemorrhages cause local inflammation of mild degree. Extravasated blood acts as a foreign substance that is destroyed and removed by absorption. Pigmentation accompanies this and varying degrees of fibrosis develop incident to the inflammatory reaction. Sometimes a large hematoma becomes encapsulated. Small hemorrhages are absorbed, leaving no local tissue alterations.

SHOCK

Clinically, the term *shock* has been applied indiscriminately to circulatory disturbances associated with weakness, pallor, stupor, rapid feeble pulse, and low arterial blood pressure. These signs may be produced by syncope, exhaustion, hemorrhage, anesthesia, primary shock, anaphylaxis, hypoglycemia, hyperthermia, cardiac failure, low atmospheric pressure, secondary shock, and by other conditions having nothing in common except the signs mentioned, including hypotension. Obviously, low blood pressure cannot be used for their differentiation.

Three major syndromes are commonly referred to as shock: *primary*, *hemor-*

rhagic, and *secondary* shock. The fact that combinations of these may occur after severe trauma has been a cause for endless confusion. Immediately after injury, primary shock may be evident; shortly the effects of hemorrhage may produce circulatory deficiency; hours later, secondary or delayed shock may develop. Thus the same injury may produce each of these syndromes, and they may coexist in varying degrees at the same time.

Primary Shock

Primary shock is a neurovascular reaction indistinguishable from syncope or fainting. It may be excited by pain, emotional reactions, or by nonsensory nerve impulses arising in traumatized tissue. Prolonged low blood pressure may be produced in animals by continuous mild electrical stimulation of afferent nerves.⁵³ Hemodilution is observed regularly, which indicates that fluid balance is not affected. Low intravascular pressure would dilute the blood by causing a shift of fluid from the tissues to the blood. Primary shock develops immediately after the injury and is usually transient unless accompanied by extensive trauma or severe hemorrhage.

Primary shock may result from fright or from trivial injuries such as a cut, vaccination, or the insertion of a needle into a vein; this is ordinary fainting. The reaction is deeper and more prolonged after wounds, burns, acute peritonitis, visceral perforation, strangulation of a loop of bowel, mesenteric thrombosis, and the like. The marked decline in blood pressure which may result from manipulation of the viscera during a surgical operation is probably due to the same mechanism. Primary shock has been reported following trauma or operation involving the fascia lata of the thigh, or even from puncture of it by a needle. The sudden collapse caused by injury to the testes is likewise neurovascular in origin. Under some of these conditions the reaction may be so deep and prolonged as to merge over into secondary shock without an interval of partial recovery.

Instances are on record in which primary shock was immediately fatal, as from extreme fright or a sudden fall into water. These deaths may have resulted from excessive neurovascular response or from adrenal cortical deficiency, as in *status lymphaticus* (see page 956).

Hemorrhagic Shock

The degree of disturbances which follow hemorrhage depends in large measure on the rapidity of the blood loss. Fifteen

to 20 per cent of the total blood volume may produce syncope if lost suddenly, whereas 30 per cent or more of the total blood volume may be lost by slow or repeated small hemorrhages before syncope occurs.

Collapse resulting from hemorrhage is characterized by weakness, pallor, decreased pulse rate, increased respiration, dizziness, sweating, a marked decline in the blood pressure, decreased blood volume and volume flow, reduction in peripheral temperature, decreased urine formation, thirst, and nausea. Vomiting seldom occurs from loss of blood per se; massive hemorrhage into the stomach regularly causes vomiting, and sometimes it follows hemorrhage into other individual areas such as ovary, testis, and certain parts of the brain.

Other features include a decrease in the plasma proteins, the erythrocytic count, and the alkali reserve. A marked reduction in the clotting time and in the flow of lymph also occurs. There is a rise in the blood sugar and frequently an increased leukocytic count. These features constitute the syndrome of *hemorrhagic shock*. The fact that several of these abnormalities occur also in *secondary shock* has led to confusion concerning these syndromes (*vide infra*). Massive or continued hemorrhages may so reduce the erythrocytic count that systemic anoxia develops. The same may result if the blood pressure remains at or below 70 mm. Hg for several hours. Anoxia causes atony, dilatation, and permeability of capillary walls; thus it may superimpose the mechanism of secondary shock upon the effects of hemorrhage.

Secondary Shock

Secondary shock is a disturbance of fluid balance resulting in a peripheral circulatory deficiency manifested by a decreased volume of blood, reduced volume flow, hemoconcentration, and by renal functional deficiency.

The basic condition in this deficiency is a disparity between the volume of blood and the volume capacity of the vascular system. Two factors contribute to the disparity: (1) Dilatation of capillaries and venules in visceral areas increases the volume capacity of the stream bed. Blood "trapped" in these vessels is out of circulation as effectively as if lost by hemorrhage. This lessens the return flow of blood to the heart thereby limiting the cardiac output and the volume flow of blood to systemic areas. The heart is a force pump, not a suction pump; it cannot draw blood to itself from the tissues but can only propel the blood which flows to it.

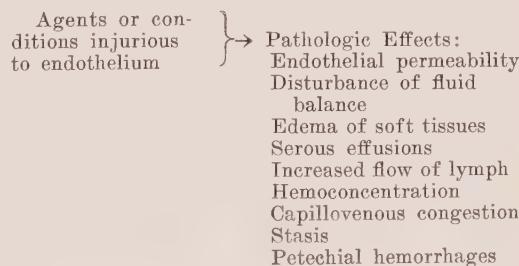
(2) As mentioned earlier (page 93), agents known as capillary poisons increase the permeability of capillary endothelium allowing the escape of fluid from the blood into the tissues. This deranges fluid balance and causes edema. The fluid lost in this way lowers the actual blood volume, increases the disparity mentioned, and leads to hemoconcentration.

There are many conditions of disease in which injurious agents may reduce the volume flow of blood and lead to shock. Harkins⁴¹ listed some thirty conditions in which shock may occur. These include trauma, burning, freezing, sunburn and radiation burns, heat stroke; anoxia from any form of asphyxia; thrombosis, intestinal strangulation, bile peritonitis, perforated gastric ulcer, pancreatitis; various poisons as mercuric chloride, arsenicals, phosphorus, phenols, venoms; anaphylaxis, transfusion reactions, systemic diseases as eclampsia, toxic jaundice; severe infections as cholera, diphtheria, pneumonia, septicemia, peritonitis, gas gangrene, and, last but not least, anesthetic agents including the barbiturates.⁵⁷ In any of these conditions the insidious development of shock may be expected. Moon^{52a, b} has verified the occurrence of shock in these conditions and in others not mentioned by Harkins. This type of circulatory failure requires time for development. It does not occur immediately after injury; hence it is called *delayed* or *secondary* shock.

Traumatic shock is not a disease entity; it represents the summative effects of several factors: primary shock, hemorrhage, anesthesia, oftentimes infections since all accidental wounds are grossly contaminated. Each of these conditions contributes to the development of secondary shock.

Surgical shock is not due to a single cause but to a combination of causes⁵⁴: the anesthetic, the local loss of blood and fluid, emotional reactions, infection or intoxication which may have reduced the patient's physiologic state, the disease itself which necessitated operation, and the absorption of toxic products from traumatized tissues. The relative importance of these factors varies in each case and they operate in varying combinations.

Circulatory Dynamics.—The principles of capillary physiology previously stated explain how various noxious agents produce circulatory deficiency. Other dysfunctions result as shown in the following diagram:



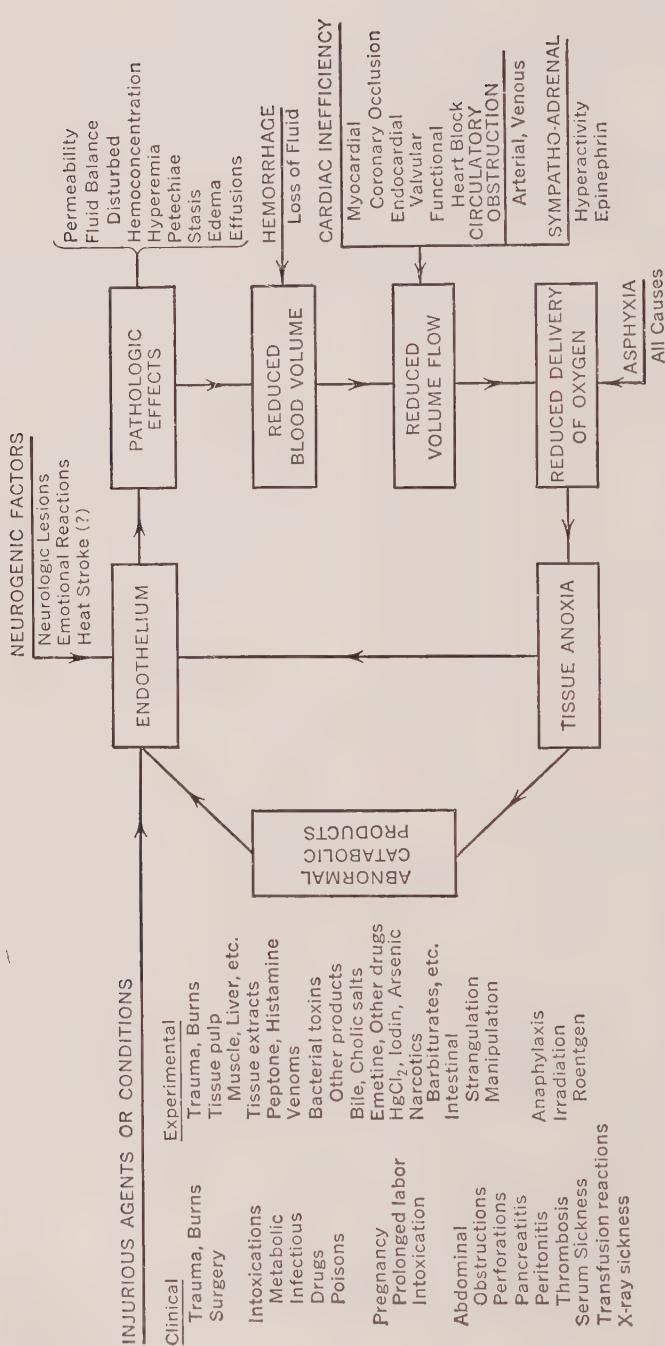


Fig. 77.—"The Cycle of Death," showing relationships between chief and contributory factors in the development of secondary shock. At the left are groups of clinical conditions which may terminate in shock; also various agents used by the author for inducing shock experimentally. (From Moon, Shock; Dynamics, Occurrence, and Management, Courtesy Lea & Febiger.)

Physiologic reactions compensate for minor degrees of circulatory deficiency. Activity of the sympatho-adrenal system causes arterial constriction, stimulates cardiac function, and causes the spleen to contract, discharging its reserve of blood into the circulation. Selective distribution of blood favors the vital organs at the expense of nonvital parts. Peripheral circulation is reduced, and the external parts become pale, cold, and almost pulseless.

So long as this compensation is effective, there is no marked decline in the arterial blood pressure but the latter is maintained at the expense of the volume flow. A reduced delivery of oxygen to the tissues follows, with accompanying anoxia which of itself increases the permeability of capillary endothelium.^{11, 12} This feature introduces a self-perpetuating factor into the mechanism, causing it to progress as a vicious circle (see Fig. 77). When finally the compensatory reactions are no longer adequate, the blood pressure declines progressively and the complete syndrome of shock is manifested clinically. Thus it is apparent that an ominously declining arterial pressure is not an early sign of shock, but it may be a sign of departed opportunity for successful treatment.

The origins and character of agents deleterious to the circulation have been investigated by methods not used hitherto.^{37, 55, 57} The mesentery or omentum of animals was exteriorized and the effects of various substances applied to or injected into the vessels were studied. When treated with fluids or plasma from anoxic tissues, the vessels became dilated and unresponsive to vasoconstrictor influences. Such substances were designated as VDM. These effects were counteracted by a vasoexcitor substance, VEM, of renal origin. Under normal conditions, VDM was inactivated or destroyed by the liver; anoxic liver lost this property and became a source for VDM. It was found that plasma from a limb on which a tourniquet had been applied, or from an animal in shock, contained much VDM. Prolonged effects of VDM rendered the arterioles and capillaries unresponsive to epinephrine and to VEM. This led to progressive venular stagnation and failure of venous return to the heart. VDM interfered with the mechanisms which compensate for a reduced blood volume. The kidneys are sensitive to lack of oxygen; under its influence they secreted no more VEM. This led to further vascular atony, greater anoxia, and the formation of more VDM in the liver. This instituted a "morbid cycle" progressing toward irreversibility. These studies confirm anoxia, vascular atony, and dilatation as major factors in the vicious circle by which shock progresses.

The chemical nature of substances responsible for capillary atony has not been determined. Green and Stoner,³⁹ found evidence incriminating adenosine and its compounds. Aub and associates³¹ showed that bacterial contamination of injured muscles produced toxic substances in the lymph collected from those muscles. Prinzmetal and associates⁴⁴ believed that shock-producing substances, resulting largely from bacterial contamination, were absorbed from the crushed muscle. It is recalled that all open traumatic wounds are grossly

contaminated, and that bacterial growth proceeds rapidly in crushed, devitalized tissues.

Tissue autolysis results in protein cleavage, the products of which may resemble peptone in their effects. The lymph collected from crushed muscle caused shock when injected intravenously into another animal.³⁴ When exchange transfusion was done between a normal and a traumatized dog, both animals developed signs of shock simultaneously.³³ Extracts of tissues after burns cause shock when injected intravenously.⁴⁵ If one member of a symbiotic pair is severely burned, his symbiotic mate will die of shock unless they are separated surgically shortly after the burn.^{38, 56} This and other evidence indicates that deleterious substances are released from traumatized or burned tissues.^{42, 52a, b}

The observations cited pertain to shock resulting from trauma or burns. However, the complete syndrome of shock may develop, without tissue injury, in a wide variety of diverse conditions (page 100). This indicates that a search for the toxic factor in shock is illogical. There are numerous agents and conditions which may produce vascular atony and thereby may cause secondary shock (Fig. 77).

Functional Effects.—Prostration is evident; the patient is profoundly depressed, weak, and restless. The pulse is rapid, feeble, and of small volume. The extremities are cold and the body temperature is low. The face is drawn, ashen, or livid in color, anxious in expression, and moist with cold sweat. The eyes are sunken and surrounded by bluish rings, producing the classical "Hippocratic facies." Thirst is incessant, but attempts to relieve it are ineffective because of vomiting. The fluid vomited is often in excess of that swallowed, and it contains brown flocculi, "coffee-grounds vomitus."

The sugar, nonprotein nitrogen, potassium content, and the viscosity of the blood are increased, its coagulability is decreased. Perspiration is excessive, thirst is constant, vomiting and diarrhea are common, urinary excretion is deficient. In the late states the blood pressure declines progressively, metabolism is low, cardiac action is rapid and weak, sensitivity and reflexes are decreased, and all functional activity is at low ebb.

Hemoconcentration, sometimes useful in detecting shock in an early stage, is shown by an increase in the erythrocytic count, the hematocrit reading, the hemoglobin content, or in the specific gravity of the whole blood. Hemoconcentration is recognized easily in experimental work and in uncomplicated cases of secondary shock in man. It indicates derangement of fluid balance, but its clinical usefulness is limited for several reasons: Instances of trauma are accompanied by hemorrhage which, by causing dilution of blood, complicates the recognition of hemoconcentration. The presence of hemoconcentration may not be suspected in an anemic subject unless a previous examination had been made, e.g., a hemoglobin content of 16 mg. might indicate hemoconcentration in the presence of anemia. Also, the introduction of fluids reduces the abnormal concentration of the blood. Hemoconcentration may subside after forty-eight hours

and moderate anemia may develop. This has been noted particularly after burns, and the author has seen it after nonfatal shock in animals.

Renal Dysfunction.—In secondary shock from whatsoever cause, oliguria or anuria develops immediately.^{52d} This may escape observation if either death or recovery occurs soon. But if circulatory deficiency persists for a few days, a progressive retention of nitrogenous wastes occurs. This syndrome of uremia, independent of pre-existing renal disease, has been reported in more than forty distinct clinical conditions. Many of the authors recognized it as a complication of sublethal shock^{32, 46, 51, 52b, d}; a few believed they were dealing with a special type of renal disease.^{35, 36, 48}

The clinical features are oliguria or anuria, erythrocytes, albumin, casts, desquamated cells and debris in the urine, and progressive retention of nitrogenous wastes leading to the syndrome of uremia. Often the patient dies from renal failure rather than from shock or its antecedent causes.

The pathologic changes were described by Adami and Nicholls²⁹ as "acute parenchymatous nephritis." The kidneys are enlarged, the cortex is swollen, edematous, and pale in contrast to the deep red medulla. Petechial hemorrhages occur in the pelvic lining and within the substance of the kidney. Microscopically, the tubular cells are swollen, granular, or vacuolated; often they have desquamated from the basement membrane. The lumina contain hyaline, granular, or pigmented casts, red cells, droplets of albumin and debris. Bowman's capsule often contains blood cells and albuminous material.

Recent observers have added few items to Adami's description. However Luck⁴⁸ reported that degeneration and necrosis involved exclusively the lower segments of the convoluted tubules; hence his designation "lower nephron nephrosis." Other observers^{32, 46, 49, 52d} have found all portions of the tubules involved; often the damage was most severe in the upper segment (see also page 588).

Imbalance of Electrolytes.—A disturbance of the normal concentration of chlorides, carbonates, phosphates, and other electrolytes occurs during secondary shock. It has been shown that the outer surface of living cells functions like a semipermeable membrane. Some vital property of protoplasm enables living cells to maintain a concentration both of anions and of cations within the cytoplasm, differing markedly from the concentration of the same ions in the vascular and interstitial fluids. This property is decreased by any type of injury to the cells and is lost entirely when the cell dies. For example, the normal differences in concentration of potassium and of sodium are approximately as follows:

$$\begin{array}{l} \text{K (cellular)} : \text{K (extracellular)} : : 20:1 \\ \text{Na (cellular)} : \text{Na (extracellular)} : : 1:30 \end{array}$$

If some agent, such as toxin, poison, or lack of oxygen, causes injury to the cells, they lose the capacity to maintain this normal difference in the concentration of electrolytes. Immediately, there occurs a movement of ions from the region of the higher to that of the lower concentration, tending to equalize them. Such

a shift will increase the potassium content of plasma and decrease its content of sodium.

A shift in other ions, both acid and basic, occurs similarly. Changes in the concentration of these ions are less in degree than those of potassium and sodium, but they result from the same mechanism and are part of the disturbance of electrolytic balance. This mechanism suggests an explanation for the blood chemical changes which develop during shock.

Many of the functional disturbances which accompany secondary shock are identical with those resulting from hemorrhages. These are outlined in Table II.

TABLE II
IDENTICAL FEATURES OF SECONDARY SHOCK
AND HEMORRHAGE

Sympatho-adrenal activity
Stimulation of myocardium
Strong rapid pulse in early stages
Peripheral vasoconstriction
Reduced volume flow
Peripheral ischemia, pallor
Loss of tissue turgor
Discharge of reservoir blood into systemic circulation
Contraction of spleen
Increased blood sugar
Dilatation of pupils, perspiration
Low basal metabolism
Declining temperature
Decreased alkaline reserve
Increased respiratory rate, thirst
Low arterial blood pressure (in late stages)
Death due to inadequate circulatory function

Because of these similarities, shock and the effects of hemorrhage have been regarded as identical.^{52e} Other features are listed in Table III and compared with the same items after simple hemorrhages.

Occurrence.—A study on the pathology of shock^{52b} was based on records and material collected by the Armed Forces Institute of Pathology, where hundreds of cases were available for study. The conditions of its occurrence among Army personnel included various forms of accidental injury, all types of severe battle wounds, surgical operations, burns, fulminating infections, poisoning with phosphorus, mercuric chloride, arsenic, alcohol, barbiturates, and other drugs, metabolic intoxications, intestinal obstruction, acute pancreatitis, peritonitis, anaphylaxis, reactions to vaccines, transfusions with incompatible blood, asphyxia with carbon monoxide, drowning, anoxia, low atmospheric pressure as in high-altitude aviation, therapeutic hyperthermia, heatstroke, and sundry instances of sudden death from causes undetermined.

TABLE III
CONTRASTED FEATURES OF SECONDARY SHOCK AND HEMORRHAGE

ITEMS	SECONDARY SHOCK	HEMORRHAGE
Endothelium	Permeable to colloids	Impermeable
Flow of lymph	Increased	Decreased
Tissue fluid	Increased	Decreased
Fluid balance	Disturbed	Undisturbed
Vomiting	Persistent	Usually no vomiting
Diarrhea	Frequent	Absent
<i>Renal:</i>		
Excretion	Deficient	Low volume
Urine:	Concentrated, low volume, albumin, erythrocytes, bile, debris	No characteristic changes
<i>Blood:</i>		
Coagulation time	Lengthened	Shortened
Concentration	Increased	Decreased
Nonprotein nitrogen	Increased	Unchanged
Potassium	Increased	Terminal increase
Plasma chlorides	Decreased	Unchanged
<i>Necropsy findings:</i>		
Edema of soft tissues	Characteristic	None
Serous effusions	Present	Absent
Capillovenous congestion	Characteristic	Absent
Petechiae	Characteristic	Absent
Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
Gastrointestinal tract	Dilated, atonic	Contracted
Parenchymal necroses	Present	Absent

Shock occurs also from eclampsia, myocardial infarction, visceral perforation as by rupture of a gastric ulcer or of the gall bladder, and from deep roentgen irradiation of the abdomen. Several agents which will induce secondary shock experimentally are listed in the diagram (Fig. 77). These produced the same pathologic features as the clinical conditions mentioned.

In many instances, as in poisoning, infection, trauma, and burns, there are obvious sources for substances injurious to capillaries; in others, the capillary atony originated from lack of oxygen; for example, shock from coronary occlusion probably results from tissue anoxia incident to impaired circulation from deficient cardiac function.

The occurrence of petechiae in the serous surfaces indicates anoxic effects on the capillaries. These are present in simple anoxia, as in strangulation, suffocation, and drowning. Their presence formerly was interpreted as a sign of asphyxial death, but they occur also from the effects of poisons and toxins upon endothelium.

Some authors disregard the systemic effects of burns, and attribute the depleted blood volume, hemoconcentration, and circulatory failure to local loss of fluid in and about the burned areas. The importance of such loss is unquestionable; its effects are proportional to the amount of fluid lost. But loss of fluid locally does not account for the intense hyperemia, edema, acute degeneration, and necrosis occurring in visceral areas remote from the burn. These indicate widespread systemic effects, logically attributed to substances derived from the burn itself. No treatise on burns will be complete unless it provides a satisfactory explanation for systemic as well as local effects.

The complete syndrome of secondary shock may develop from therapeutic hyperthermia,⁴⁴ heat stroke,⁵⁰ and from heat exhaustion. Clinically it is accompanied by temperatures ranging from 107° to 110° F., and by convulsions and other evidence of neurological disturbances; postmortem examination regularly shows widespread degenerative processes in the brain.⁵⁰

These observations suggest two possibilities; perhaps the excessive heat produces degenerative changes in the brain and that these cause atony of capillaries and circulatory deficiency like that resulting from local injuries, hemorrhages, or infections in the brain. The alternate possibility is that capillary endothelium may be damaged by temperatures in the range mentioned, as they are damaged by other noxae. This would explain the congestive and edematous changes seen in the viscera, but not the widespread degeneration found in the brain.

Aviators often developed severe or fatal shock after flights at 35,000 feet or higher, even though abundant oxygen was supplied artificially. The clinical features, including hemoconcentration, were characteristic of secondary shock. A marked reduction of external (atmospheric) pressure would cause dilatation of capillaries and venules, and would tend to draw fluid from the blood into the tissues. Apparently the forces which govern the movement of fluid between the blood and the tissues are unable to maintain normal fluid balance when external atmospheric pressure is greatly reduced. Necropsy examination in such cases^{52b} showed intense hyperemia and edema of the viscera and degenerative changes both in the brain and in parenchymatous organs as described below.

Morphologic Changes and Sequelae.—The first published report on the pathology of shock recorded two types of changes in the visceral organs. One of these was indicative of endothelial damage, as described on page 93. It included dilatation and engorgement of capillaries and venules in the thoracic, abdominal, and cranial viscera, petechiae in serous and mucous surfaces and within parenchymatous organs, effusions in serous cavities, and edema of soft visceral tissues (Fig. 75). Congestion and edema of the somatic portions of the body are rarely seen. The origin of these changes was set forth in the discussion of the capillaries (page 93).

The other characteristic change was acute parenchymatous degeneration and necrosis, involving chiefly the kidneys (Fig. 78), liver, and heart. It is suggested that the same injurious agents which damage endothelium, causing capillary dilatation and permeability, likewise cause degeneration and necrosis of organs. This is exemplified in the effects of various poisons, infections, and in severe metabolic intoxications. But the same effects result from asphyxia and in deaths from hyperthermia, low atmospheric pressure, and from uncomplicated anoxia. No source for a toxic agent is apparent under these circumstances. This indicates that endothelial, renal, hepatic, and myocardial cells are delicately susceptible to lack of oxygen and that degenerative changes occur rapidly—even within a few minutes—when the supply of oxygen is insufficient.

Pulmonary hyperemia and edema are almost constant features after death by shock. These are more intense in the posterior portions because of gravity.

The lungs are increased in weight by 100 to 200 per cent. When circulatory failure has progressed rapidly to death in a few hours, hyperemia is intense but the edema is less pronounced than when death has been delayed twenty-four hours or longer. Grossly, the lungs do not collapse readily; the color is a deep cyanotic red, somewhat mottled in distribution. Petechial hemorrhages often are seen in the pleurae and in other serous surfaces. On section, blood-tinged frothy fluid exudes readily under pressure. When edema is marked, the lung often resembles a blood-soaked sponge. Microscopically there is engorgement of the capillaries and venules both in the alveolar septa and in the bronchial mucosa (Fig. 75). Edema fluid is present in the interstitial tissue and is prominent in the alveolar spaces. Small extravasations of blood, capillary hemorrhages, are frequent.

When death has been delayed forty-eight hours or longer, the development of secondary or terminal pneumonia occurs almost regularly. Lungs in which the circulation is impaired and the spaces filled with albuminous fluid will almost certainly develop secondary pneumonia if neither death nor recovery occurs soon.

HYPEREMIA

Hyperemia refers to an increased amount of blood within the finer vessels of a tissue. The term is used synonymously with *congestion*.

Active hyperemia implies congestion due to an increased flow of arterial blood to the part. During functional activity of any tissue, a larger supply of blood is required by it. This is supplied by arterial dilatation controlled by vasomotor reactions. The flushing of the skin in response to emotions, and in the radiation of excess heat, is active hyperemia. Another instance is the congestion which develops in the early stage of inflammation.

Passive hyperemia results from obstruction or hindrance to the onward flow of venous blood from a part. This often follows defective cardiac action, as valvular regurgitation or myocardial inefficiency, causing congestion of blood in the pulmonary circulation and, later, in

systemic areas. Systemic passive congestion may arise also from obstruction to the pulmonary circulation. Chronic diseases of the lungs such as tuberculosis, bronchiectasis, emphysema or various forms of pneumoconiosis (*q.v.*) obstruct the flow of blood through the pulmonary capillaries. This obstruction causes hypertrophy of the right ventricle, *cor pulmonale* (see Chapters 19 and 23) and subsequent varying degrees of systemic passive hyperemia. The gross and microscopic features of this are as described below.

seen in the lumina of the bronchi. These changes are most marked in the posterior and dependent portions because of the effect of gravitation upon the blood and the edema fluid. The bronchial mucosae are congested, cyanotic, and swollen. If passive congestion is marked in degree and of long duration, the lungs on section have a brownish color due to hematogenous pigmentation.

Microscopically, there is engorgement of the veins and capillaries. The alveolar walls are edematous and increased in thick-

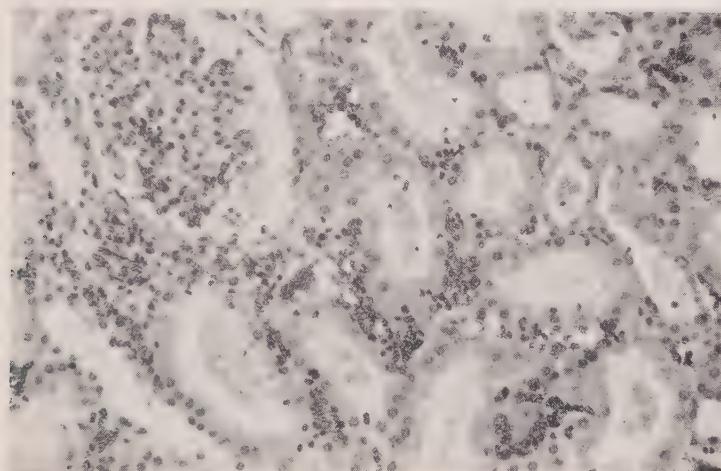


Fig. 78.—Hyperemia and parenchymatous degeneration of renal cortex after death from burns. The necropsy was made one hour after death.

Causes for local passive hyperemia include the pressure of a tumor, enlarged gland, aneurysm, inflammatory mass, ligature, scar tissue or of other abnormality upon a vessel. A pregnant uterus or the head of the fetus sometimes presses upon the iliac vein, producing passive congestion in the leg. The formation of a thrombus within a vein has a similar effect. A loop of bowel sometimes becomes twisted upon itself, as a volvulus, and by obstructing the venous flow produces passive hyperemia of the loop. The same result may follow herniation. A bandage, tourniquet, or garter may obstruct the venous return flow from a limb.

The effects of passive congestion are seen most characteristically in the lungs and in the liver. Grossly, the lungs are increased in weight and have a deep cyanotic-red color. Blood-tinged frothy fluid escapes from the cut surfaces and may be

ness. Edema fluid containing a high percentage of albumin is present in the alveoli. Within this fluid varying numbers of erythrocytes and monocytes are found. The latter usually contain granules of brown pigment and, because of their association with passive congestion, are known as "heart failure cells." The bronchial lumina contain similar fluid and cells, often mixed with mucus and desquamated epithelium.

Passive hyperemia produces a cyanotic appearance of the liver. It is increased in size and weight, purplish-red in color, and the capsule is tense. The lobular markings are accentuated. This is very marked on cut surfaces and may be seen through the capsule. It produces a fine mottling to which the descriptive term "nutmeg liver" is applied. Microscopically, the centers of the lobules are deeply congested, the sinusoids are dis-

tended with blood, and necrosis may have involved the cells adjacent to the central veins. The cells in the peripheral zones show degeneration which may be either parenchymatous or fatty. This renders these zones pale in contrast to the deep congestion of the centers, and produces the fine lobular mottling seen grossly. Varying amounts of hematogenous pigment are present.

Passive hyperemia of other tissues is accompanied by similar congestion of the veins and capillaries, by degenerative changes in the cells, pigmentation, and by edema. Prolonged passive congestion often leads to a diffuse proliferation of fibrous tissue which renders the organ firm or tough in consistency. This, accompanied by hematogenous pigmentation, is called *brown induration*. It is seen characteristically in the lungs, liver, and spleen. Some cardiac functional deficiency is usually the cause for this condition.

The term *congestive heart failure* is used by clinicians to designate cardiac failure from sundry causes. It should be limited to such and should *not* be applied to pulmonary hyperemia and edema resulting from endothelial rather than from cardiac causes.

Capillovenous Hyperemia.—This term has not been used by pathologists hitherto. It is introduced here to designate a form of congestion, of common occurrence, resulting from atony of the walls of the capillaries and venules. Under the influence of injurious agents of various kinds, the endothelium of the finer vessels relaxes, becomes atonic, the vessels dilate and become engorged with blood. This condition develops incident to severe intoxications of all kinds, either extraneous or endogenous in origin, and incident to a deficient local supply of oxygen—anoxia. The viscera become deeply and diffusely congested, the organs have a dusky cyanotic appearance like that of acute passive congestion, and dark blood oozes and drips from such organs as the lungs, liver, and kidneys when they are sectioned. The bowels are relaxed, atonic, the peritoneal and mucosal surfaces have a bluish-red or dusky appearance, and the venules along the mesenteric attachment are tortuous, engorged, and unusually prominent. Frequently

there are capillary hemorrhages in mucous and serous surfaces. Blood-tinged albuminous fluid often is found in the serous cavities.

Capillovenous congestion is seen characteristically in the thoracic and abdominal viscera after death from asphyxia, from acute poisoning as with arsenic or mercury, from infections of unusual severity, from abdominal catastrophes as rupture or strangulation of the bowel, from burns, anaphylaxis, and from secondary shock from other causes (Fig. 75).

The gross appearance of the tissues is identical to that in acute passive hyperemia, and that term hitherto has been applied regularly to the viscera when capillovenous congestion was present. The difference in these conditions lies in the mechanisms by which they are produced. Passive hyperemia results from obstruction or damming back of the venous circulation, while capillovenous hyperemia results from atony and relaxation of the capillaries and veins.

Microscopic examination shows capillaries and venules distended with masses of closely packed corpuscles (Fig. 76). Albuminous fluid is seen in the tissue spaces, minute extravasations of red cells are common, and acute granular degeneration has affected the parenchymatous cells.

Functional Effects.—Active hyperemia is accompanied by increased oxidation and functional activity. This is a normal accompaniment of physiologic activity. Likewise, the active hyperemia of inflammation is associated with increased oxidation and temperature, but other factors than hyperemia are concerned here.

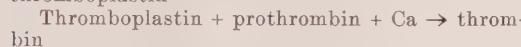
Passive hyperemia is accompanied by a decrease in circulation, metabolism, and functional efficiency in the areas affected. The capillary blood pressure is increased and oxygen supply is diminished. Endothelial permeability plus high capillary blood pressure produce edema. The same effects result from capillovenous hyperemia. Pulmonary congestion and edema from either cause predispose to terminal pneumonia.^{52c}

The term *stasis* is applied to stagnation of the circulation in local areas. It affects chiefly the capillaries and venules and results either from passive or capillovenous hyperemia. It is accompanied by

increased permeability of the endothelium, which allows the plasma of the blood to escape into the tissues, producing edema. This leaves the corpuscles in densely packed masses within the lumina. Stasis tends to become irreversible if not relieved soon.

COAGULATION OR CLOTTING OF BLOOD

The clotting of blood is a protective physiologic mechanism of highest importance. Without it, trivial injuries or bleeding incident to other causes would result in extensive or fatal hemorrhages. The mechanism by which an almost frictionless fluid is converted rapidly into a tough elastic solid mass—the clot—is complex; it includes several factors present in normal blood, i.e., prothrombin, thromboplastinogen, ionized calcium, fibrinogen, and platelets. In its simplest terms, the process of clot formation is as follows:



The clotting mechanism is activated by injury to platelets, causing them to act upon the thromboplastinogen present in normal plasma, converting it into thromboplastin. A similar conversion occurs when blood comes in contact with injured tissue. The mucoid ground substance of vessel walls contains a potent and speedy activator of thromboplastinogen.⁵⁸ Immediately as thromboplastin is formed or released, it converts prothrombin into thrombin which, in turn, converts fibrinogen into fibrin.

Minute threads of fibrin form about the injured platelets or the damaged vascular wall. More platelets are attached, more fibrin forms, blood cells are enmeshed in its threads, forming a thrombus or clot.

Thrombin not only changes fibrinogen into fibrin, it also causes the disintegration of platelets thereby producing more thrombin. This initiates a "chain reaction" between platelets and thrombin, thereby speeding the formation of fibrin. Any agent or condition which removes or inhibits the action of thrombin breaks this chain reaction and reduces the formation of fibrin. In such a state the platelets do not clump readily nor disintegrate—a condition found in hemophilia. Here the dysfunction is due to deficient formation of thromboplastin, resulting in insufficient production of thrombin.

Another result of the disintegration of platelets is the liberation of a vasoconstrictor substance which causes gradual and sustained contraction of vascular walls and is an important factor in hemostasis. This vasoconstrictive effect may prevent serious or fatal bleeding in those who have a congenital absence of fibrinogen or other deficiency of the clotting mechanism.

This complex mechanism is further complicated by secondary factors. Quick⁷² has shown that prothrombin is not a single sub-

stance but contains two components, one of which, A, disappeared from stored plasma. The other, B, can be absorbed on aluminum hydroxide.

Factor A of prothrombin was reported independently by several workers; it is referred to as *labile factor*, or *accelerator globulin*. It is not influenced by deficiency of vitamin K nor by Dicumarol, but any diminution of the labile factor decreases the conversion of prothrombin into thrombin and thus reduces or retards clot formation. Factor B possesses the classical qualities of prothrombin. It is diminished in certain forms of congenital prothrombin deficiency, in vitamin K deficiency, and in poisoning with Dicumarol.

A reaction involving so many factors is subject to abnormalities or deficiencies in those several factors. Thus a deficiency of thromboplastin may result from lack of thromboplastinogen, or of platelets, or from inhibition of the platelet enzyme. Two conditions are exemplary of these lacks: True *hemophilia* is due to a congenital deficiency of thromboplastinogen. In *thrombocytopenia* the lack of platelets causes deficient formation of thrombin; hence low coagulability and the tendency to bleed. For further data on these conditions, see pages 875 and 901.

Since all the factors for fibrin formation are present in normal blood, spontaneous clotting might occur except for some inhibitory mechanism. The work of Howell⁶⁶ and his collaborators indicated that heparin, a potent anticoagulant, is the normal antithrombic agent which preserves the fluidity of the blood. He demonstrated an increased amount of heparin in the blood during peptone and anaphylactic shock and believed this caused the delayed clotting in these conditions. Heparin has a powerful antithrombic effect when injected into the blood stream. However, Quick has indicated that heparin merely intensifies the antithrombic activity of the plasma albumin.

Dicumarol is a potent noncoagulant agent found in spoiled sweet-clover hay.⁶⁹ When given orally or intravenously, it causes a progressive decrease of prothrombin in the blood. It is used therapeutically to prevent clotting; overdoses cause death with severe hemorrhagic manifestations. *Hirudin*, extracted from the salivary glands of leeches, and certain venoms as of the cobra and several varieties of *Bothrops*, inactivate prothrombin and thus inhibit clotting of the blood.⁶²

Thrombosis

Since the mechanism of clotting is initiated by degeneration or injury to endothelium, clot formation often occurs *within the vascular system*. A clot formed within the lumen of a vessel or within the heart is called a *thrombus*, and the process is known as *thrombosis*. Reports on the frequency of thrombosis indicate that it is found in from 6 to 24 per cent of autopsies after death from various causes. Because of its frequency, the number and variety of its causes, and the gravity of

its sequelae, thrombosis is a pathologic condition of high importance.

Thrombi consist of platelets, fibrin, erythrocytes, and leukocytes; the relative proportions of these vary depending on accompanying conditions and on the rapidity of the clot formation. When the blood flow is rapid and the speed of thrombosis is slow, the thrombus may consist almost entirely of platelets. Such thrombi form on the heart valves in rheumatic fever. They are small, pale, firm, and not easily detached. When blood flow is slow or stagnant and clotting is rapid, the proportion of the elements may be identical to that found in circulating blood. Clots containing much fibrin and

and even up the vena cava for varying distances. This extension is usually proximally with the flow of blood, but, if the vessel is obstructed, the thrombus may propagate distally as well (Fig. 79).

Postmortem Clotting.—After death, the blood in the heart and in the great vessels may clot. When this occurs promptly after death, the masses are deep red throughout, described as "currant jelly" clots. When clotting is slow, as after secondary shock from various causes, the erythrocytes settle by gravity and leave a supernatant layer of plasma. The lower portion is a deep red and the upper part is pale yellowish or grayish-white, sometimes called "chicken fat" clot.

It is important to distinguish postmortem clots from true thrombi. The former are moist, tough in consistency, and are easily separated



Fig. 79.—Thrombosis of a large vein and its tributaries. (AFIP No. 30192.)

erythrocytes are called *red thrombi*. A minute examination shows an anastomosing framework of riblike structures or corrugations, known as the lines of Zahn. These begin in the area where thrombosis began, which is the paler portion, and extend into the mass of propagated clot. They consist chiefly of agglutinated strands of platelets and leukocytes with masses of erythrocytes and fibrin between the strands.

A thrombus may propagate from its point of origin in a vein to the junction with a larger vein. Thus, a thrombus developing in a pelvic vein may extend along the tributaries to the common iliac vein

from the vessel wall. They are not laminated but are homogeneous, and do not contain rib-like corrugations; the intima beneath them is smooth and glistening. Antemortem thrombi tend to be dryer, often they are brittle or friable, and they are adherent to the vessel wall; when separated, the intima beneath them is dull or mottled, and the lines of Zahn can be seen grossly; microscopically, the coral-like structure of the framework is clearly distinguishable. Usually the thrombus is pale, dry, and firm at its point of origin or "head," while the body or tail, formed by propagation, may be red and tough; this portion of a thrombus may resemble a postmortem clot.

Causation of Thrombosis.—Conditions contributing to thrombosis are (a) injury or degeneration of the vessel wall; (b)

toxic effects; (c) infection or inflammation; (d) stasis, slowing, or eddying of the blood stream; (e) increased coagulability of the blood.

a. An injury which bruises tissues deeply may damage vascular walls even though they are not torn or broken; thrombosis may develop where the intima was bruised. This is a frequent complication of fractured limbs or other severe *traumatic injuries*. When a vessel has been ligated or clamped in the course of surgical operation, thrombosis is initiated at that point. Thrombosis of the axillary veins may result from indirect trauma or strain resulting from strenuous muscular exertion. Degeneration of the intima, as in areas of *atherosclerosis*, may be followed by thrombus formation. However, the blood flow in the aorta is so swift that these thrombi seldom become large. Sclerosis of veins, as in *hemorrhoids* and other *varicosities*, may result in thrombosis. In *cardiac infarction* from coronary occlusion, a large thrombotic mass often forms on the endocardium, over the infarcted area. These are called *mural thrombi*. Sometimes such a thrombus may become *pedunculated* and hang out so far as to obstruct a valvular orifice; or it may be detached and lie free within a cardiac chamber, a *ball thrombus*. A detached mural thrombus in the right ventricle may block a large branch of the pulmonary artery, causing fatal *pulmonary embolism*.

b. Certain chemical poisons such as arsenicals, mercurials, and potassium chlorate may cause thrombosis. A similar effect has been reported in mushroom poisoning. The venom of certain snakes, as Russell's viper, cause prompt intravascular clotting. It appears that the venoms of different species vary widely in their effects in this particular; some hasten clotting, others inhibit it, and others do not affect it notably (see review by Essex⁶²). Toxins formed within the body, as in eclampsia, may be accompanied by thrombosis; a similar effect has been attributed to burns. This, however, is doubted and the suggestion is made that the thrombosis observed resulted from direct injury to superficial veins by heat; or from local sepsis following the burns.⁴² The clotting time of the blood

is lengthened after severe burns; hence burns do not, *per se*, predispose to thrombosis.

c. Inflammation of the vessel wall, from whatsoever cause, will produce thrombosis almost regularly. Thrombophlebitis, thromboarteritis (Buerger's disease), and periarteritis nodosa are instances of vascular inflammation of unknown origin resulting in thrombosis. It commonly happens that the vessels adjacent to any local acute infection become involved by the spreading inflammation. The vessel wall becomes inflamed and the intima is roughened; platelets adhere to it, become agglutinated, and the clotting mechanism is initiated.

Often the infection penetrates the wall and the organisms invade and multiply in the thrombus. This contributes both to the extension of the thrombus and to the spread of the infection, and is known as *septic thrombosis*. Infected thrombi tend to soften, liquefy, and disintegrate; septic emboli are carried to the lungs, causing pulmonary abscesses and septicemia. Puerperal sepsis may result in thrombosis of the pelvic veins; the clot propagates into the larger vessel and may even cause obstruction of the iliac veins. A similar process may involve the lateral sinus from infection about the middle ear, or the cavernous sinus from suppurative processes about the face, nose, or orbit, with similar results. This is known as *sinus thrombosis* (Fig. 80).

Septic thrombosis may develop from deep wounds or acute infections in various locations. Appendiceal abscess or suppuration elsewhere in the abdomen causes thrombosis in branches of the portal vein; emboli from these carry the infection to the liver, resulting in *portal pyemia*. Other sequelae of thrombosis are discussed under Infarction, page 114.

d. Slowing, stasis, and eddying of the blood flow are highly important causes for thrombosis. Since the blood flow is more rapid and direct in arteries, thrombosis occurs more frequently in veins. Where the blood flow swirls or eddies, as in the auricular appendages or in aneurysm of an artery or of the heart, a laminated thrombus may form on the lining. This occurs regularly in large arterial aneurysms, and occasionally in the dilated area formed by a healed

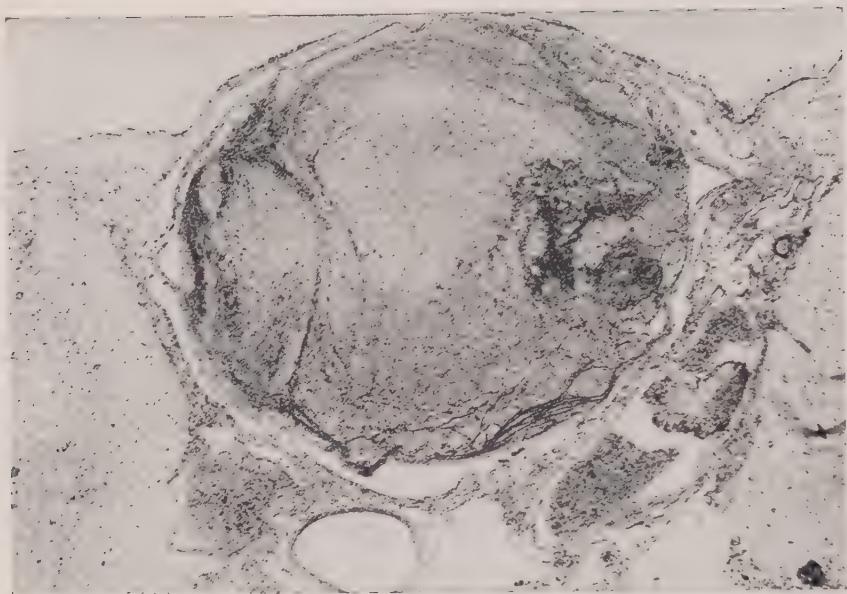


Fig. 80.—Recent thrombosis of the superior longitudinal sinus. (AFIP No. 72741.)



Fig. 81.—Thrombosis of a coronary artery followed by organization and canalization. Thrombosis probably resulted from atherosclerosis which is seen in the artery wall. (AFIP No. 64135.)

cardiac infarct. In such instances, injury of endothelium by stretching is probably a factor.

Varicose dilatation of veins often is complicated by thrombosis. Varices of the superficial veins of the leg, of the pampiniform plexus (*varicocele*), and of the perirectal veins (*hemorrhoids*) are common instances.

Postoperative thrombosis occurs in a vessel which has been ligated; a column of blood becomes static and the ligature may damage the wall enough to initiate clotting. But major surgical operations may be complicated by thrombosis in vessels which have not been ligated or injured. Wounds and hemorrhages are followed by an acceleration in the clotting time, perhaps due to the medullary hormone of the adrenal glands. Complete inactivity after operation causes the venous blood flow to become sluggish. This favors clotting of blood which is likely to occur in the large veins of the pelvis, the iliacs, and in the femoral veins.

Thrombosis of the veins mentioned may occur also during prolonged illness such as typhoid, tuberculosis, or cancer. It is believed that this results from sluggish venous blood flow as described above. The pressure of a tumor, or that of the head of the fetus in utero, upon a large vein may be followed by thrombosis in the stagnant column of blood. Slowing of the systemic blood flow due to cardiac lesions resulting in passive hyperemia, produces a tendency to thrombosis.

e. Increased coagulability of blood, from whatever cause, predisposes to thrombosis. The discharge of adrenalin into the circulation is an instance. This occurs during fright, anger, after wounds, and after hemorrhage. Physiologically it is a protective mechanism tending to prevent excessive hemorrhage after injury. A rare condition known as *panthrombosis* involves the veins in various parts of the body. The etiology of this is obscure; an increased tendency of the blood to clot has been suggested as a cause. Increased coagulability also results from the introduction of certain foreign substances, as venoms, foreign sera, or extracts of tissues. This group of causes is relatively unimportant as compared with those discussed under a, c, and d.

Thrombi often form in the lumina of the capillaries and venules locally in areas of injury or of acute infection. These may impair the local circulation but they are of minor significance as compared with thrombi in large vessels.

Results of Thrombosis.—The occlusion of a vein by a thrombus causes stasis of blood in the area drained by that vein. This results in acute passive hyperemia, edema, and even necrosis of the affected tissues. Thus, thrombosis of the veins of the thigh may cause gangrene of the leg and foot. *Mesenteric thrombosis* causes gangrene of the bowel. The affected part becomes cyanotic red, then purple, then almost black. It swells enormously and peristalsis is interrupted; severe pain and signs of intestinal obstruction accompany this. Thrombosis of the veins or arteries of the appendix results in gangrenous appendicitis, which is more rapid in development and more grave than the suppurative form. Surgical relief must be prompt and effective in these gangrenous conditions if fatal results are to be avoided.

Thrombotic varices, as in the rectal area or in the superficial veins of the leg, may cause local necrosis resulting in ulcerated hemorrhoids or varicose ulcers.

The effects of detached thrombotic masses are discussed under *embolism* and *infarction*. When the thrombus remains in situ, a process of organization develops from the lining of the vessel. Capillaries bud out into the thrombotic mass, fibroblasts proliferate, gradually the mass is absorbed and replaced by organized tissue as in the repair of any injury. During organization one or more vascular channels often are formed, with partial re-establishment of the circulation; this is called *canalization* (Fig. 81). In other instances the vascular lumen is obliterated by a fibrous scar. Sometimes the thrombus itself or the scar becomes calcified, producing what is known as a *phlebolith*. This occurs after thrombosis in varicose veins of the leg more often than elsewhere.

Embolism

Particles of substances, such as fragments of thrombi, tissue cells, clumps of bacteria, parasites, globules of fat or of air, carried by the blood stream, are called *emboli*. Fragments may be detached from vegetations on a valve, or from a

thrombus in any location, and be swept along with the current until the vascular lumen becomes so small that the particle obstructs it completely. The thrombus which formed when a vein was ligated during an operation, or by stasis during severe illness, may be dislodged by a movement of the part or by activity of the patient. This is a common cause for death by pulmonary embolism. A similar effect may occur from the ligated umbilical cord of an infant. Manipulation or massage of an area where thrombophlebitis is present may loosen thrombotic masses into the blood stream. Portions of mural thrombi within the heart often are detached and carried by the arterial blood. Likewise, fragments of thrombi within aneurysmal sacs or upon atheromatous patches may become emboli.

Venous emboli originate in peripheral venous channels and lodge in the lungs. A venous thrombus, when carried as an embolus to the lungs, may cause death with dramatic suddenness if it is large enough to obstruct the main pulmonary artery leading to one lung or even to one lobe. Numerous instances are on record in which a patient convalescing from typhoid fever or from surgical operation, sat up or walked a few steps. The physical exertion dislodged a thrombus from the pelvic or other large veins, with results immediately fatal. Smaller venous emboli may produce infarcts of the lung or may have little demonstrable effect if the circulation in the lung is otherwise normal.

Arterial emboli originate from the heart, as fragments of mural or valvular thrombi, or from thrombotic masses in aneurysmal sacs or upon atheromatous patches in large arterial trunks. In rare instances a pulmonary vein may become thrombosed and a portion of the thrombus may pass through the left heart into the systemic arterial circulation.

A patent foramen ovale may allow a venous embolus to enter the arterial circulation, or vice versa. These cases of *paradoxical embolism* are not common. Variations in blood pressure in different parts of anastomosing venous channels may result in *retrograde* or paradoxical embolism. Batson⁵⁹ has demonstrated a plexiform group of veins within the spinal canal. These communicate with the large veins of the thoracic and abdominal cavities at each vertebral level. These veins are protected from external pressure by the walls of the spinal canal, while those in

the body cavities are subject to wide variations of pressure. Accordingly, blood from the pelvic veins may be driven, by increased pelvic pressure, into the intraspinal vessels and their tributaries which drain the vertebral bodies. Emboli originating in the pelvic, abdominal, or thoracic regions may be carried in a retrograde direction into cranial or spinal regions. This mechanism may explain the common occurrence of vertebral metastases from tumors, as prostatic carcinoma, in the pelvic region. Coman and de Long⁶⁰ confirmed this mechanism experimentally. Other instances of paradoxical embolism may have a similar explanation.

The effects of embolism depend upon the size and nature of the embolus, the organs involved, and upon the presence of anastomosing arterial circulation. If the embolus lodges in an area having an anastomosing arterial circulation, as in the somatic parts of the body, the effects may be insignificant. In the absence of a collateral arterial blood supply, the area of tissue supplied by the obstructed artery will become necrotic promptly. Minute emboli may produce little change unless they are infected.

INFARCTION

An *infarct* is a local area of necrosis resulting from vascular obstruction. An uninfected embolus causes simple necrosis of the area nourished by the involved artery. The venules and capillaries dilate when deprived of circulation, blood flows into them from the network of anastomosing venules in the surrounding tissue, so that the recently formed infarct is swollen and has a deeply congested or even hemorrhagic appearance. Diffuse hemorrhage results from dissolution of capillary walls when deprived of oxygen. In soft tissues, such as lung or bowel, the infarcts are usually hemorrhagic. Parenchymatous cells swell after necrosis occurs. In firm tissue such as the kidney, this swelling presses out the blood contained in the minute vessels and the area becomes pale. These are called *anemic infarcts*. Regularly, such an infarct, when fresh, is surrounded by a narrow zone of hyperemia, due to dilatation of minute vessels adjacent to the necrotic tissue.

Infarcts are irregular in shape, corresponding to the distribution of the involved artery. When fresh they are swollen, congested, or pale, and have sharply defined hyperemic margins. Those in lung tissue have a deep cyanotic red

color and are firm because the extravasated blood which has filled the alveolar spaces is coagulated. At first these infarcts are moist, and blood oozes from them on section. After a day or two they become dry and firm. Later, organization begins about the margins; eventually the area becomes a soft pigmented scar. Infarcts in kidneys show as areas of necrosis with varying degrees of cytolysis and of fibrous tissue proliferation, depending on the duration of the lesion. In the early stage, microscopic examination shows a narrow zone of living renal tissue beneath the capsule. This zone has received sufficient blood, via the capsular vessels, to prevent necrosis. Gradually the necrotic parenchyma is absorbed, and fibrosis results in

branch is the most common cause for sudden death; smaller areas heal by fibrosis. Sometimes an infarcted area of myocardium ruptures, causing massive hemorrhages into the pericardial sac followed immediately by death.

Infarction of the brain may result from embolism or from sclerosis of a cerebral artery; the middle cerebral or its branches are most commonly involved. The infarcted area undergoes softening and liquefaction; glial proliferation about the margins produces a tough elastic wall. Eventually such a lesion has the characteristics of a cyst filled with turbid or clear fluid, depending on the age of the process. The pathologic effects will depend on the location of the infarct and upon its size.



Fig. 82.—Massive infarctions of the spleen due to emboli from vegetative endocarditis.

a dense scar in which hyalinized glomeruli are recognizable. Old infarcts show as depressed contracted scars. These are often seen in the spleen and kidneys associated with "vegetative" endocarditis. Large splenic infarcts usually are pale (Fig. 82); smaller ones may be hemorrhagic. Absorption of necrotic substance and fibrosis occurs in splenic as in renal infarcts.

Infarction of cardiac muscle is a frequent result of occlusion of a coronary arterial branch. In this instance, arteriosclerosis, with or without thrombosis, is usually the cause. The result depends largely upon the area of muscle rendered anemic. Occlusion of a large coronary

A functional disturbance of the central nervous system usually follows, but, since any portion of the brain may be involved, the manifestations cannot be predicted.

Occlusion of an artery or vein by thrombosis, by pressure or by twisting, may cause infarction. This is seen in thrombosis of a mesenteric vein, or when a loop of bowel becomes twisted upon itself, in strangulation of the bowel from any cause, in torsion of the spermatic cord, and in other similar conditions. Infarction of an intestine from any cause produces signs of obstruction. Death by shock usually results unless surgical intervention is prompt and effective.

The development of gangrene of an extremity, due to arteriosclerotic occlusion

of its arteries, is essentially the same process as infarction of organs. Whether this will result in dry or moist gangrene depends upon the circumstances and conditions. Necrosis of the toes or of the foot resulting from thromboarteritis obliterans is essentially a process of infarction. Periarteritis nodosa often causes thrombotic obstruction of small arteries and may produce infarcts in the kidneys or elsewhere.

Septic Infarction.—Emboli from simple thrombosis are usually uninfected, and the resulting infarcts are called *bland*. Emboli may be derived from infected thrombotic material and may cause multiple areas of infection elsewhere, as described under septic thrombosis.

bolism. Experiments⁷³ have shown that rather large amounts of fat, as 2 ml. per kilogram, were required to produce fatal effects in dogs. A corresponding amount for man might be about 150 grams. A dosage of 0.9 ml. per kilogram was fatal in rabbits.⁶⁵

Most instances of fat embolism result from trauma, particularly from fractures. Warren⁷⁷ reviewed the records and tissues from 100 cases occurring in young healthy males—Army personnel. Of these, 91 followed fractures, of which 82 per cent were of the femur, tibia, or both; others resulted from burns and from poisoning. MacMahon and Weiss⁷⁰ reported a case in which fat embolism occurred after poisoning with carbon tetrachloride. Degeneration and necrosis liberated much fat from hepatic cells; this readily entered the radicles of the hepatic veins and was carried by the venous blood to the lungs.

Most authors agree that the conditions necessary to cause fat embolism are (1) fat mobilized by trauma, infections, burns,⁷⁶ or poisons, (2)

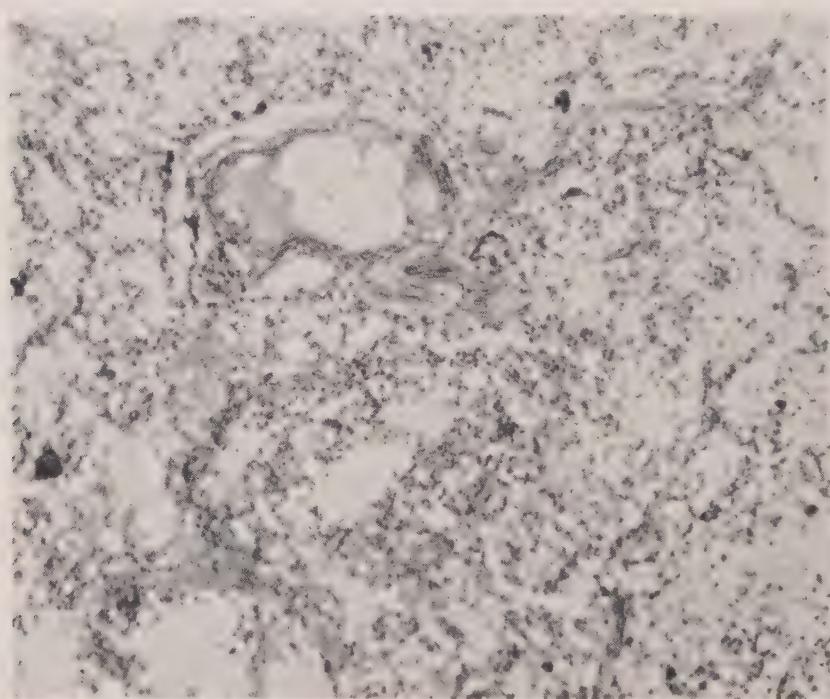


Fig. 83.—Photomicrograph of lung showing fat emboli in an artery and in capillaries, marked hyperemia, and edema. (AFIP No. 82674, courtesy Dr. Shields Warren and Am. J. Path. 22: 69, 1946.)

FAT EMBOLISM

Neutral fat from traumatized tissue or bone marrow sometimes gains access to the circulation. Extrinsic fat or oil, introduced for therapeutic or other purposes, may produce similar effects. Such fats, carried by the blood stream, may obstruct capillaries in the lungs, brain, or elsewhere. This constitutes fat em-

bolism. Experiments⁷³ have shown that rather large amounts of fat, as 2 ml. per kilogram, were required to produce fatal effects in dogs. A corresponding amount for man might be about 150 grams. A dosage of 0.9 ml. per kilogram was fatal in rabbits.⁶⁵

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venous circulation. Dyes injected into the marrow appear in the systemic circulation almost as quickly as if given intravenously. If fatty marrow is liquefied by trauma, much of it may enter the circulation directly, independent of local pressure. Clumps of marrow cells have been found along with fat in the pulmonary capillaries, indicating the source of the fat in these cases.

The effects of fat embolism result chiefly from obstruction to capillaries in the lungs and in the brain. Death from fat embolism may result within minutes, hours or days, depending probably upon the volume of fat which entered the circulation. Interference with the pulmonary circulation results in asphyxia accompanied by capillary permeability, hyperemia and petechiae in the lungs, pleurae, pericardium, and conjunctivae. Regularly the lungs are heavy; Warren reported the average combined weight as 1,600 grams. The factor of anoxia brings into play the mechanism of secondary shock which presents many of the clinical and pathologic features of fat embolism. With routine stains, conspicuous vacuoles will be found in the pulmonary arterioles, capillaries, and often in the alveolar spaces; pulmonary edema (Fig. 83) is prominent. Vacuoles may be numerous in the renal glomeruli. The use of a fat stain, as Sudan IV in frozen sections, will determine the presence of fat.

Cerebral manifestations predominate in about 25 per cent of cases. The gross findings here include petechiae in the leptomeninges and minute focal hemorrhages throughout the brain. Small anemic infarcts and areas of softening are seen microscopically, together with perivascular edema and hemorrhages. Here, as in the lungs, the changes as well as the clinical signs may be indistinguishable from those of shock.

Fat emboli are usually found in the renal glomeruli, but the observation has been made that renal effects have not resulted. Probably this refers to sequelae following recovery. In those cases in which circulatory deficiency and anoxia continue for several days, one would expect renal deficiency to develop as it does in sublethal shock.

AIR EMBOLISM

Under unusual circumstances, air may be drawn or forced into the circulation in amounts sufficient to cause serious disturbances.⁶⁴ When a large vein adjacent to the chest is opened, the negative pressure produced by inspiration may draw air into the proximal portion even though the distal end is bleeding freely or has been clamped. Air may be introduced accidentally when inducing pneumothorax. In rare cases, forcible insufflation of the vagina during pregnancy has resulted in air embolism.

The air tends to lodge in the right ventricle, where it mixes with the blood, forming a foamy mass which may obstruct the flow. Large thrombotic masses in the ventricle have resulted from experimental air embolism. When death from this cause is suspected, the heart should be opened under water *in situ* so that the presence of air in it may be shown. The signs of disturbed circulation are like those of fat embolism, but it

is questionable whether bubbles of air may pass through the pulmonary capillaries and affect the cerebral circulation.

CAISSON DISEASE

When divers or workers in caissons are brought from the high atmospheric pressure of the caisson to normal atmospheric pressure, severe disturbances often result. The amount of gases such as oxygen, carbon dioxide, and nitrogen held in solution in the cells and tissues increases under high barometric pressure. When the pressure is reduced, the gases come out of solution as minute bubbles within the cells and fluids. This effect is like that seen in a flask of carbonated water when the stopper is removed. The bubbles in the plasma coalesce and increase in size; if the period of high pressure has been long and the decompression rapid, these bubbles may produce serious air embolism.

Exactly the same effects are produced in high altitude aviation. At 34,000 feet the barometric pressure is only one-fourth that at sea level; an aviator rising to that height is subject to the same relative decompression as a diver rising from a depth of 100 feet of water. The effects of rapid decompression became an unexpected hazard in aviation, not obviated by supplying oxygen artificially.

The oxygen and carbon dioxide released by decompression are soon resorbed or eliminated by respiration, but nitrogen is less soluble and its removal is much slower. The effects of nitrogen emboli vary with the location. The "bends" are severe cramplike pains in the abdomen, trunk, and limbs; this feature is attributed to the plugging of small vessels in these regions by nitrogen bubbles. The "stagers" consist of behavior like that of a thoroughly drunken person, due to cerebral effects. The "chokes" consist of severe burning or stabbing substernal pain which is accentuated by deep respirations. The subject suffers air hunger but the pain causes shallow and rapid breathing. This may be followed by collapse, unconsciousness, and death with manifestations of shock. This feature is ascribed to pulmonary nitrogen embolism. The "itch" is irritation of the skin by the same mechanism.

The manifestations described may be relieved or prevented by very gradual decompression of caisson workers or by recompressing them temporarily if the symptoms are acute. The remedy among aviators is a return to earth. This however, is not always possible under combat conditions.

The most prolonged effects of caisson disease are seen in the ends of long bones where infarction has resulted from nitrogen embolism. The repair of these is slow and incomplete; they become impregnated with calcium and cast a dense, sharply defined x-ray shadow. This condition produces signs of a deforming arthritis, with collapse or depression of the articular surfaces of weight-bearing bones;⁶⁵ this may produce permanent disability. Phemister⁷¹ described one case of massive infarction in the tibia, of thirty-five years' duration; the findings were confirmed at autopsy.

References

Fluid Balance

- Best, C. H., and Taylor, N. B.: *Physiological Basis of Medical Practice*, ed. 5, Baltimore, 1950, Williams & Wilkins Co., pp. 20-23 (water balance, dehydration).
- Chambers, R.: *Ann. New York Acad. Sc.* **49**: 549, 1948 (fluid exchange).
- Elkington, J. R.: *Ann. Rev. Physiol.* **12**: 145, 1950.
- Gamble, J. L.: *Extracellular Fluid (Lecture Syllabus)*, Boston, 1942, Spaulding Moss Co.
- Gaunt, R., Birnie, J. H., and Eversole, W. J.: *Physiol. Rev.* **29**: 281, 1949.
- Rogers, L.: *Cholera and Its Treatment*, London, 1911, Oxford University Press.

Edema

- Chambers, R., and Zweifach, B. W.: *Physiol. Rev.* **27**: 436, 1947 (capillary permeability).
- Drinker, C. K., and Yoffey, J. M.: *Lymphatics, Lymph and Lymphoid Tissue*, Cambridge, 1941, Harvard University Press.
- Ebbecke, U.: *Arch. f. d. ges. Physiol.* **199**: 197, 1923; *Klin. Wchnschr.* **2**: 1725, 1923 (capillary reactions).
- Heidenhain, R.: *Arch. f. d. ges. Physiol.* **49**: 209, 1891 (formation of lymph).
- Krogh, A.: *Anatomy and Physiology of the Capillaries*, ed. 2, New Haven, 1929, Yale University Press.
- Landis, E. M.: *Physiol. Rev.* **14**: 404, 1934; *Am. J. M. Sc.* **193**: 297, 1937 (capillary pressure and permeability).
- Lewis, Thos.: *Blood Vessels of the Human Skin and Their Responses*, London, 1927, Shaw & Sons.
- Moon, V. H.: *Arch. Path.* **26**: 132, 1938 (infection); *Am. J. Path.* **24**: 249, 1948 (low atmospheric pressure).
- Starling, E. H.: *Human Physiology*, ed. 8, London, 1907, J. & A. Churchill (capillary poisons).

Hemorrhage

- Adolph, E. F.: *Physiol. Rev.* **13**: 336, 1933 (distribution of fluids).
- Adolph, E. F., Gerbasi, M. J., and Lepore, M. J.: *Am. J. Physiol.* **105**: 502, 1933 (hemorrhage).
- Castle, W. B., and Minot, G. R.: *Pathologic Physiology and Clinical Description of the Anemias*, New York, 1936, Oxford Press.
- Chambers, R., and Zweifach, B. W.: *Am. J. Anat.* **75**: 173, 1944; *Am. J. Physiol.* **150**: 239, 1947.
- Ebert, R. V., Stead, E. A., and Gibson, J. G.: *Arch. Int. Med.* **68**: 578, 1941 (effects of blood loss in man).
- Goldblatt, H.: *The Harvey Lectures* **33**: 237, 1937-1938 (hypertension from renal ischemia).
- Goormaghtigh, H. N.: *Am. J. Path.* **16**: 409, 1940 (juxtaglomerular apparatus).
- Heymans, C.: *New England J. Med.* **219**: 147, 1938 (carotid sinus).
- Price, P. B., Hanlin, C. R., Lengmire, W. P., and Metcalf, W.: *Bull. Johns Hopkins Hosp.* **69**: 327, 1941 (effects of acute hemorrhage).
- Robertson, J. D.: *J. Physiol.* **84**: 393, 1935 (restoration of blood volume).
- Selye, H.: *Endocrinol.* **21**: 169, 1937; *J. Clin. Endocrinol.* **6**: 117, 1946 (alarm reaction).
- Shenkin, H. A., Cheney, R. H., Govons, S. R., Hardy, J. D., Fletcher, A. G., Jr., and Starr, Isaac: *Am. J. M. Sc.* **208**: 421, 1944 (effects of blood loss in man).
- Wallace, J., and Sharpey-Schafer, E. P.: *Lancet* **2**: 393, 1941 (effects of blood loss in man).

Shock

- Adami, J. G., and Nicholls, A. G.: *Principles of Pathology*, vol. 2, Philadelphia, 1909, Lea & Febiger, pp. 740-743.
- Atchley, D. W.: *New England J. Med.* **213**: 861, 1935 (renal effects of shock).

- Aub, J. C., Brues, A. M., Dubos, R., Keiley, S. S., Nathanson, I. T., Pope, A., and Zamecnik, P. C.: *War Med.* **5**: 71, 1944 (infection).
- Bell, E. T., and Knutson, R. C.: *J. A. M. A.* **134**: 441, 1947 (renal effects of shock).
- Best, C. H., and Solandt, D. Y.: *Am. J. Physiol.* **133**: 213, 1941 (exchange transfusion in experimental shock).
- Blalock, A.: *Bull. Johns Hopkins Hosp.* **72**: 54, 1943; *Principles of Surgical Care; Shock and Other Problems*, St. Louis, 1940, The C. V. Mosby Co.
- Bywaters, E. G. L.: *J. A. M. A.* **124**: 1103, 1944 (crush syndrome).
- Bywaters, E. G. L., and Beall, D.: *Brit. M. J.* **1**: 427, 1941 (traumatic azotemia).
- Chambers, R., Zweifach, B. W., Lowenstein, B. E., and Lee, R. E.: *Proc. Soc. Exper. Biol. & Med.* **56**: 73, 1944; *Ann. Surg.* **120**: 791, 1944; *Am. J. Physiol.* **150**: 239, 1947.
- Christophe, L.: *La mort des brûlés*, Paris, 1939, Masson et Cie (burns, symbiosis).
- Green, H. W., and Stoner, H. B.: *Biological Action of Adenosine Nucleotide*, London, 1950, H. K. Lewis & Co.
- Gregersen, M. I.: *Ann. Rev. Physiol.* **8**: 335, 1946 (review).
- Harkins, H. N.: *Surgery* **9**: 449 *et seq.*, 1941.
- Harkins, H. N.: *Surgery* **9**: 231, 447 and 607, 1941 (shock, review); *Treatment of Burns*, Springfield, 1942, Charles C Thomas.
- Harris, K. E.: *Heart* **14**: 161, 1927 (toxic substance in burned skin).
- Hartman, F. W., and Major, R. C.: *Am. J. Clin. Path.* **5**: 392, 1935 (shock from hyperthermia).
- Heilbrun, L. V., and others: *Physiol. Zoöl.* **19**: 404, 1946 (toxic factor in burns).
- Herbut, P. A.: *Ann. Int. Med.* **25**: 648, 1946 (renal effects of shock).
- Jeghers, H., and Bakst, H. J.: *Ann. Int. Med.* **11**: 1861, 1938 (renal effects of shock).
- Lucké, B.: *Mil. Surgeon* **99**: 371, 1946 (lower nephron nephrosis).
- McManus, J. F. A.: *Medical Diseases of the Kidney*, Philadelphia, 1950, Lea & Febiger, pp. 87-94.
- Malamud, N., Haymaker, W., and Custer, R. P.: *Mil. Surgeon* **99**: 397, 1946 (heat stroke).
- Mallory, T. B.: *Am. J. Clin. Path.* **17**: 427, 1947 (renal effects of shock).
- Moon, V. H.: (a) *Shock, Its Dynamics, Occurrence and Management*, Philadelphia, 1942 Lea & Febiger.
(b) *The Pathology of Secondary Shock*, *Am. J. Path.* **24**: 235, 1948.
(c) *Arch. Path.* **26**: 132, 1938 (terminal pneumonia).
(d) *Renal Deficiency in Shock*, *J. A. M. A.* **134**: 425, 1947.
(e) Moon, and others: *J. A. M. A.* **117**: 2024, 1941 (shock vs. hemorrhage).
- Pheister, D. B., Laester, C. H., Eichelberger, L., and Schachter, R. J.: *Ann. Surg.* **119**: 26, 1944 (primary shock).
- Prinzmetal, M., Freed, S. C., and Kruger, H. E.: *War Med.* **5**: 74, 1944 (infection in shock).
- Shorr, E., Zweifach, B. W., and Furchtgott, R. F.: *Science* **102**: 489, 1945.
- Vogt, E.: *Ztschr. f. exper. Path. u. Therap.* **II**: 191, 1912 (burns symbiosis).
- Zweifach, B. W., and others: *Surgery* **18**: 48, 1945 (barbiturates in shock).

Clotting, Thrombosis, Embolism

- Abul-Haj, S. K., and others: *Science* **114**: 237, 1951 (thromboplastin).
- Batson, O. V.: *Am. J. Roentgenol.* **48**: 715, 1942 (vertebral vein system).
- Coman, D. R., and deLong, R. P.: *Cancer* **4**: 610, 1951 (retrograde embolism).
- Dam, H.: *Nature* **133**: 1909, 1934; *Lancet* **1**: 720, 1938 (vitamin K).
- Essex, H. E.: *Physiol. Rev.* **25**: 148, 1945 (venoms).
- Fanti, P., and Nance, M.: *Nature* **158**: 708, 1946 (clotting).
- Fulton, J. F.: *Science* **95**: 207, 1942 (air embolism).

65. Harris, R. J., Perrett, T. S., and MacLocklin, A.: *Ann. Surg.* **110**: 1095, 1939 (fat embolism, experimental).
66. Howell, W. H.: *J. A. M. A.* **117**: 1059, 1941 (clotting).
67. Howell, W. H., and Holt, E.: *Am. J. Physiol.* **47**: 328, 1918 (clotting).
68. James, C. C. M.: *Lancet* **2**: 6, 1945 (caisson disease).
69. Link, K. P., and others: *Proc. Fed. Soc. Exper. Biol.* **4**: 176, 1944; *Harvey Lectures* **39**: 162, 1943-44 (Dicumarol).
70. MacMahon, H. E., and Weiss, S.: *Am. J. Path.* **5**: 623, 1929 (fat embolism).
71. Phemister, D. B.: *Arch. Surg.* **41**: 1455, 1940 (caisson disease).
72. Quick, A. J.: (a) *Am. J. Physiol.* **140**: 212, 1943; **151**: 63, 1947.
(b) *Am. J. M. Sc.* **214**: 272, 1947 (clotting of blood).
73. Simonds, J. P.: *J. A. M. A.* **69**: 883, 1917 (fat embolism, experimental).
74. Tocantins, L. M.: (a) *Am. J. Physiol.* **114**: 709, 1936; **139**: 265, 1943; *Blood* **1**: 156, 1946 (clotting, thrombocytopenia).
(b) *Proc. Soc. Exper. Biol. & Med.* **45**: 292, 1940.
75. Troland, C. E., and Lee, F. C.: *J. A. M. A.* **111**: 221, 1938 (thrombocytopenia).
76. Wakely, C. P. G.: *Surgery* **10**: 207, 1941 (burns—fat embolism).
77. Warren, S.: *Am. J. Path.* **22**: 69, 1946 (fat embolism).
78. Wright, R. B.: *Ann. Surg.* **96**: 75, 1932 (fat embolism).
79. Zucker, M. P.: *Am. J. Physiol.* **158**: 387, 1949 (congenital deficiency of fibrin).

Chapter 6

PHYSICAL AGENTS IN THE CAUSATION OF INJURY AND DISEASE

ALAN R. MORITZ

INJURIES CAUSED BY FORCE (MECHANICAL ENERGY)

Force or mechanical energy is that which changes or tends to change the state of rest or uniform motion of matter. When a harmful change in the state of rest or motion of the components of the body has been caused by force, a mechanical injury is said to have been sustained.

The most common manifestation of such an injury is a disruption in the continuity of tissue or a wound. The force responsible for the production of a wound is usually liberated incident to a collision between the body and some external mass and may be derived from the motion of the body itself, from the motion of the other participant in the collision, or from both.

Physical Principles

The kinetic energy or wound-producing capacity which an object has in consequence of its motion is determined by its weight and velocity. In the case of simple forward motion this force may be computed by the formula $MV^2/2g$ in which M equals weight in pounds, V the velocity in feet per second, and g the acceleration of gravity or 32 feet per second.

In addition to the kinetic energy of forward motion an object may possess energy by reason of the fact that it is rotating on its own axis. Such energy is frequently possessed by a flying missile and provides a particularly significant accretion to the wound-producing capacity of a bullet discharged from a rifled barrel. The extra energy possessed by an object having this type of motion may be calculated from the formula $IW^2/2g$ in which I equals the rotary inertia or $\frac{Mr^2}{2}$ (r = radius of cross section and

M = weight), W the angular velocity in radians per second or 2π times number of rotations per second, and g the acceleration of gravity or 32.

By both of the above formulas the force available for wound production has been calculated in terms of foot pounds, this unit being an amount of work capable of raising a weight

of one pound through a vertical distance of one foot against the force of gravity. It is apparent from these elementary calculations that the kinetic energy of a moving object tends to increase arithmetically in relation to its weight and geometrically in relation to its velocity.

Thus, if each of two objects, one weighing twice as much as the other, is traveling at the same velocity, the kinetic energy of the former will be twice that of the latter. However, if they weigh the same but one is traveling twice as fast as the other, its energy will be four times as great.

It should not be inferred that the kinetic energy and the wound-producing force of mass in motion are necessarily identical. Obviously it is only that part of the total energy of motion that is actually utilized in changing the state of rest or uniform motion of the tissues that is capable of contributing to injury production. Unexpended force possessed by the source of energy after the impulse of collision is still capable of doing work and has not contributed to injury production. Force of impact utilized to induce uniform motion of the tissues or to displace or to deform the object that has struck or has been struck by the tissues is likewise noninjurious since it has been expended for work other than that of disturbing the uniform state of rest or motion of the tissues.

The duration of impulse or period of energy transfer is an important factor in determining how much of the force of an impact will be expended in the causation of uniform or noninjurious motion and how much in the causation of nonuniform or potentially injurious movement of the tissues. Every athlete is aware of the desirability of prolonging the duration of impulse. To diminish the amount of force likely to be expended in the production of nonuniform or disruptive movement of tissues the tumbler rolls with his fall, the ballplayer moves his gloved hand with the caught ball, and the fighter endeavors to move with his opponent's blow.

Protracted deceleration probably accounts in large measure for the occasional and seemingly miraculous survival of persons who have fallen from great heights and for the relative immunity of relaxed, drunken persons and infants to injury from falls that would ordinarily be regarded as dangerous.

Another important factor in determining the wound-producing^{*} capacity of an impact is the

size of the surface area to which the force is applied. The larger the area through which a given amount of impact force is transmitted, the less will be its intensity. Thus, an impulse of a certain number of foot pounds might cause uniform tissue displacement without injury when acting over a large area and yet be capable of causing severe disruption of tissue when acting through an area comparable to the edge or point of a knife.

Many other factors may modify the disruptive effects of impacts even though they be similar in respect to the amount of energy expended, the duration of impulse, and the area of collision contact. One of these is the extent to which the force may be intensified by lever action or by hydrostatic effect. A small force applied near the end of a lever will be greatly intensified as the fulcrum is approached. This phenomenon is particularly important in relation to the production of fractures of long bones. Similarly a relatively small compression of a large hollow viscous may displace a sufficient volume of fluid to rupture the wall of a less voluminous communicating structure. Differences in the elasticity, plasticity, or inertia of tissues are of great importance in respect to whether or not a given force will produce disruptive change. Liver is ordinarily more friable and more readily disrupted by distortion than is lung or muscle. A hyperplastic and friable spleen may be torn to pieces by an impact that would be harmless to a normal spleen. The capillary fragility of persons suffering from certain vitamin deficiencies is often greater than that of the normal individual.

The foregoing discussion of the mechanics of injury production by the energy of motion has concerned disruption of tissue or wound production. Although a wound is the most common, it is by no means the only manifestation of injury caused by the energy of motion. Force has been defined as that which changes or tends to change the state of rest or uniform motion of matter. The application of force to the surface of the body may alter subsurface relationships sufficiently to cause severe functional disturbance even though no wound be produced.

Thus, the application of pressure in many situations may cause harmful interference with the function of the compressed tissue even though the force be insufficient to produce a wound. Mechanical obstruction of the air passages for more than a few minutes is likely to cause death from systemic anoxia. A tight tourniquet applied for thirty minutes may result in ischemic necrosis of an extremity.

Other injurious effects of the energy of motion that have only recently been appreciated include the hemodynamic disturbance that may be induced by rapid acceleration or deceleration incident to air travel. The inertia of man's body opposes any change in the rate or direction of its motion. In a rapidly moving plane this inertia is partially overcome by the seat or other apparatus that tends to coordinate the motion of the occupant with that of the plane. The cohesion of the solid elements of man's body is such that their deceleration or acceleration in such circumstances is ordinarily not

sufficiently nonuniform as to be disruptive. However, the blood within the vascular system is not bound to follow the changes in rate or direction of motion of the plane as closely as do the solid components of man's body. The inertia of the blood tends to cause it to remain within that part of the vascular bed that is hindmost in the case of linear acceleration, that is foremost in the case of linear deceleration, and that is farthest from the center of the turn in the case of a change in direction of flight.

Although rapid linear acceleration may occur when a plane is catapulted into the air and rapid deceleration may occur during a braked landing, the force exerted by these maneuvers is rarely of sufficient magnitude to produce significant physiologic disturbances. Of greater importance are the disturbances that occur when the flight of a plane is altered from a straight line. The force exerted on man's body in such circumstances varies inversely with the radius of the curved path of flight and directly with the square of the plane's speed.

The magnitude of this force is computed by the equation $F = \frac{V^2}{32r}$ in which F is expressed in multiples of normal gravitational force (g), V = velocity in feet per second, and r = radius of turn in feet. Thus, a force of 2.6g would be exerted on the pilot of a plane that was moving at a velocity of 500 feet per second in a curve having a radius of 3000 feet. If the pilot normally weighed 180 pounds, he would weigh 468 pounds at 2.6g and the weight of all his tissues and fluids would remain increased as long as high-velocity flight in a curve is continued.

If the orientation of the occupant's body in relation to the direction of force is such that inertia prevents blood from entering or remaining within the head, a force of between 6 and 8g may cause unconsciousness and even death. If the orientation is such that the inertia causes blood to accumulate and remain in the head, a force as little as 3g may cause severe and protracted disturbance.¹

Local Effects of Mechanical Violence

WOUNDS

As previously indicated, a wound is a mechanically produced interruption in the continuity of tissue. There are several anatomic types of such disruptive lesions, for which distinctive terms are used.

Abrasions.—An abrasion or scratch represents the tearing away of epidermal cells by friction. Such a defect may or may not penetrate to the corium. Although an abrasion may provide a portal of entry for infection, such a wound is ordinarily of little significance beyond the fact that it provides objective evidence that force has been applied to the surface of the body. The direction of

motion responsible for an abrasion can frequently be recognized by the manner in which the partially detached sheets of epidermis have been rolled on themselves at the distal end of the defect. In some instances the nature of the abrading object can be recognized by the distribution and configuration of the epidermal defects.

that bridge the ends of the defect in order to recognize it as a laceration. In the case of curved or angular lacerations of the skin, the apex of the angle or the convexity of the curve will face the direction from which the force was applied.

The force of an external impact may cause laceration of internal structures without damage to the skin or sub-

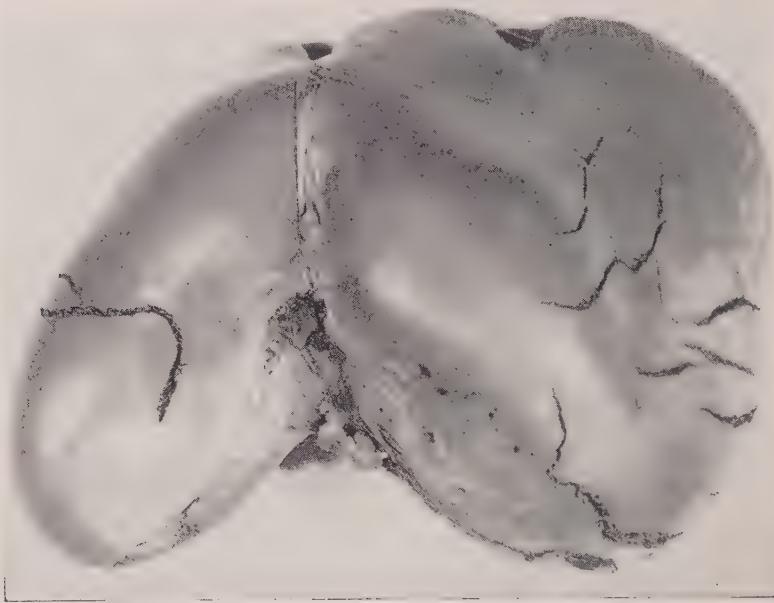


Fig. 84.—Multiple lacerations of liver caused by lateral compression of thorax. There were no external wounds or fractures. Death resulted from intra-abdominal hemorrhage.

Laceration.—A laceration represents the effects of excessive stretching of the tissue, and, although any tissue may be disrupted in this manner, such injuries involve the integument most commonly and particularly where it is stretched over bone as in the hands or over the skull. Lacerations of skin caused by the unidirectional displacement and stretching which occurs incident to the impact of an obliquely directed force are likely to be linear or curved, whereas those produced by the multidirectional radial displacement of a more vertically acting crushing impact are frequently stellate and characteristically have ragged margins. In the former type of laceration the tissue may be so cleanly disrupted as to resemble an incised wound. In such a circumstance it may be necessary to identify the attenuated strands of tissue

cutaneous tissue. Thus, ligaments, muscles, or blood vessels are frequently lacerated by excessive stretching with or without superficial injury. Compression of fluid or gas in hollow viscera may cause laceration and rupture of their walls. Soft tissues adjacent to the site of a fracture are usually lacerated by the broken ends of the bone.

Contusion.—A simple contusion or bruise is an injury in which the force of an impact is transmitted through the skin to the underlying tissues with sufficient intensity to disrupt the walls of small blood vessels and to cause interstitial bleeding without disruption of the epidermis.

Usually the interstitial bleeding is so visible through the skin. However, a superficial as to be almost immediately

bruise may be so deep that either hours elapse before the extravasated blood becomes superficial enough to be visible or it is never seen from the surface. An external impact may cause extensive bruising of internal viscera without damage to the skin or subcutaneous tissue.



Fig. 85.—Contusion of myocardium with extensive interstitial hemorrhage. Blunt impact of thorax incident to automobile accident. Immediate death. ($\times 375$.)

Different individuals vary enormously in respect to their susceptibility to mechanical disruption of small blood vessels. Persons suffering from certain dietary deficiencies and blood dyscrasias are likely to sustain remarkable extensive contusions as a result of relatively mild impacts.

Incision.—An incised wound is one produced by the pressure and friction against the skin of an object having a sharp edge. In this type of injury the tissues are uniformly displaced to either side of the cutting edge with the result that the primary damage is largely limited to the immediate vicinity of the defect.

Penetrating Injury.—The impact of any appropriately shaped resistant object against the skin may produce a defect so deep and of such relatively small diameter that its outstanding characteristic is penetration. Slender sharp objects and flying missiles are the most common causes of such injuries. Although the majority of penetrating wounds involve the skin and subcutaneous tissue, the broken end of a bone often causes penetrating injury without involving the integument.

Fractures.—It is obvious that any force which tends to change the state of uniform motion or rest of the body is likely to disrupt its least plastic tissue, this being the bony skeleton. A fracture is a mechanically produced disruption in the continuity of bone. Such osseous defects vary from the simple linear break caused by excessive bending, to the explosive comminution caused by the impact of a high-velocity projectile. Of particular importance in the mechanics

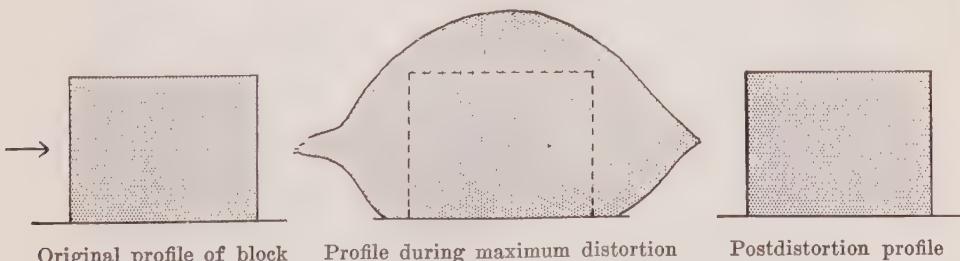


Fig. 86.—Impulse of high-velocity projectile transmitted to gelatin block. Lateral view of block before, during, and after being distorted by the force of a high-velocity projectile which passed through it centrally from end to end. Diagrammatic reproductions from a series of shadowgraphs made by Black, Burns, and Zuckerman. When the elasticity and inertia of the various components of such a mass differ as they do in the case of living tissue, lacerations and fractures remote from the path of the bullet are likely to occur. (From Black, A. M., Burns, B. D., and Zuckerman, S.: Brit. J. Med. 2: 872, 1941.)

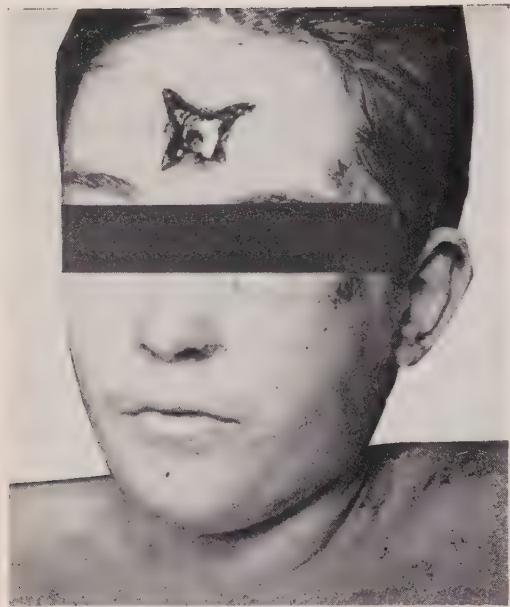


Fig. 87.—Stellate entrance wound caused by the propulsion of rapidly expanding gases into the tissues. The muzzle of the gun was in contact with the skin at the moment of firing.

of fracture production is the transmission of force from the site of external application and its intensification at a distant point through lever action. It should not be assumed that the stress responsible for a fracture is necessarily of unusual magnitude or of external origin. A relatively minor stress may cause a diseased bone to break. Fractures of normal bones may result from violent and uncoordinated internal stresses imposed by convulsive muscular contractions.

Bullet Wounds.—Injuries produced by gunfire have certain peculiar and important characteristics by reason of the velocity of the wounding missile. The extent of such an injury is characteristically much greater than would be expected from the diameter of the bullet. The force of the impulse is projected radially from the path of the bullet with such intensity that it may and usually does cause a cylindrical zone of disruptive change in the tissues that surround the main tract of the wound. Thus, blood vessels may be lacerated or bones may be fractured at a considerable distance from the path of the bullet. One of the most commonly encountered manifestations of radially transmitted forces from bullets is the comminution

A.



B.

Fig. 88.—Arteriovenous injury, bullet wound. Edge of laceration in femoral vein (A) and near-by femoral artery (B) six days after injury. An arteriovenous aneurysm probably would have developed if the patient had survived. ($\times 50$)

of the orbital plates that occurs so frequently in association with transcerebral injury by high-velocity projectiles.

Another peculiar feature of injuries by gunfire is the creation of one or several secondary wounding missiles in the event that the bullet strikes a bone. The fragments of shattered bone tend to be propelled in a cone-shaped course in the direction of the flight of the bullet. Each fragment becomes a separate destructive foreign body. It is characteristic of bullet wounds of bones that the defect tends to be conical. The hole of entrance in a bone is characteristically smaller than that of exit.

If the muzzle of a gun is in contact with or very close to the skin at the moment of fire, the rapidly expanding gases may enter the tissues with explosive effects. If the structure of the tissue is such that the explosive force can be decompressed internally, as is likely to be the case with wounds of the chest or abdomen, the skin wound may not be significantly modified. If, however, the tissue is compact and the shot was fired at contact range, the skin will usually be extensively lacerated in a stellate fashion.

Close inspection of bullet wounds in the skin will usually serve to establish whether they represent wounds of entrance or wounds of exit. When a bullet first strikes the body, it displaces and stretches the skin and tends to produce a funnel-shaped defect by passing through it. The diameter of the defect in the epidermis is usually greater than that in the dermis. The dermal hole is characteristically smaller than the bullet that produced it and is surrounded by a narrow zone from which the epidermis is abraded. The diameter of the epidermal defect is ordinarily a closer approximation of that of the bullet than is the hole through the dermis.

When a bullet leaves the body it is traveling at a slower speed and is frequently tumbling. Instead of producing a punched-out exit wound, it usually produces an irregularly lacerated wound, the edges of which are everted and the dimensions of which are usually considerably greater than those of the entrance wound. Inspection of the surface of an exit wound will fail to disclose the marginal abrasion of epidermis that characterizes an entrance wound.

In the case of bullet wounds produced by close-range but not contact fire, various other alterations of the skin in the region of the entrance wound may result from the muzzle blast of smoke and flame. Recognition of burning or of powder deposits may be of great medicolegal importance in relation to the range of fire. Recovery of a bullet or of fragments of a bullet may also provide important medicolegal evidence.²

OTHER LOCAL MANIFESTATIONS OF MECHANICAL INJURY

In the normal course of events the mechanical disruption of living tissue is attended and followed by various local disturbances, the nature of which depends in part upon the site and severity

of the disruptive lesion and in part upon the capacity of the organism to react.

Hemorrhage.—Hemorrhage is an immediate and inevitable sequel to mechanical disruption of living vascularized tissue. Blood continues to flow from the damaged vessels until prevented from doing so by thrombosis, by vasoconstriction, or by equalization of intra- and extravascular pressure through a drop in the former or a rise in the latter.

In the case of damage to the small vessels (capillaries, arterioles, venules), vasoconstriction is a more important mechanism than thrombosis in the induction of hemostasis. This is also true when vessels are lacerated or crushed, whether they be large or small. When any vessel is incised or injured in such a manner that the disturbance is limited to the site of the defect, hemostasis is more dependent on the occurrence of thrombosis.

In noncommunicating injuries such as may occur with fracture or other forms of internal laceration, the opposition offered by the surrounding intact tissue to the accumulating mass of extravascular blood is an important mechanism of hemostasis. When exsanguination has been severe or when injury has caused a state of shock, the fall in systemic blood pressure contributes to other factors in preventing further loss of blood.

Mechanical disturbances resulting from an accumulation of blood in an extravascular situation may be caused by distention, compression or obstruction. One of the outstanding manifestations of distention of tissue by hemorrhage is pain. The first evidence of the accumulation of a relatively small amount of blood beneath the periosteum or immediately below the peritoneum may be pain. There is probably no pain more exquisite than that caused by the expansion of the outer layers of the aorta by blood incident to the formation of a dissecting aneurysm.

The most important compressive effects of extravasated blood are those seen in relation to intracranial and intrapericardial hemorrhage. The rapid accumulation of as little as 100 c.c. in the former situation or 300 c.c. in the latter may be fatal by its compressive effect. That the rate of hemorrhage is an important factor in determining such a mechanical effect is revealed by the fact that considerably larger amounts of blood can be tolerated in either situation if it has accumulated slowly. In the case of a slowly developing subdural hemorrhage, several hundred cubic centimeters may accumulate before signs of increased intracranial pressure became apparent. If the pericardium is distended slowly, several thousand cubic centimeters of fluid may be tolerated without the occurrence of fatal cardiac tamponade.

One of the best examples of obstructive disturbance caused by extravasated blood in con-

tradistinction to compression may occur when several hundred cubic centimeters of blood escape rapidly into the lower air passages. The foam created by mixing blood and air in such a situation may be sufficiently obstructive to cause death by suffocation.

The preceding paragraphs have been concerned with early mechanical disturbances caused by the accumulation of blood in an extravascular situation. The possibility of late mechanical disturbances due to secondary edema incident to the presence of blood in tissue spaces should not be ignored. One of the best

of hemorrhage are the pigmentary changes. As the oxyhemoglobin is reduced, the color of the injured tissue changes from red through purple to blue. In the case of small extravasations the erythrocytes are either ingested by phagocytes and transported from the site of injury or the products of their disintegration *in situ* are carried away by the lymph so rapidly that secondary pigmentary changes are not perceptible. If the mass of extravasated blood is large or if its disposal is delayed by inadequate lymph flow, the iron is separated from the globin after hemolysis *in situ* and the pigment



Fig. 89.—Powder stippling of skin around entrance wound of bullet fired at close but not at contact range. The distance between muzzle and target at the moment of fire was great enough (6 to 12 inches) to suggest that the manner of injury was accident or murder rather than suicide.

examples of this phenomenon is provided by the progressive expansion of a subdural hematoma. Although the space originally consumed by such a hemorrhage may fail to cause a significant amount of cerebral compression, the subsequent imbibition of fluid by the hematoma sometimes gives rise to a progressively incapacitating or even fatal rise in intracranial pressure.

Chemical injury may be superimposed on mechanical injury if the removal of extravasated blood from the tissues is delayed sufficiently that the erythrocytes deteriorate *in situ*. A striking feature of the deterioration of blood at the site

is subsequently converted to bilirubin and biliverdin, with chromatic changes ranging through yellow, green, and brown. In addition to these changes in color, two types of crystalline derivatives of hemoglobin may be identified on microscopic examination, hematoidin and hemosiderin. (See page 82 for further discussion of hemoglobin pigments.)

Aseptic Inflammation.—Unless the injury is almost immediately fatal, the occurrence of a mechanical disruption of living cells is followed by a series of

secondary local reactive changes that comprise the phenomenon of aseptic inflammation. These reactive changes may occur in response to any one or any combination of several effects of the trauma.

One of these is the liberation of reaction-eliciting substances from the disrupted cells. Just why protoplasm extruded from a living cell into the intercellular spaces should be harmful to its intact neighbors is not clear. Some of the released substances which alter the permeability and caliber of capillaries and attract leukocytes are probably polypeptides that result from the local interruption of protein catabolism. Whatever their nature, it is clear

to the mass of tissue destroyed mechanically may result in a severe and extensive inflammatory reaction because of secondary ischemic necrosis of cells that were not originally disturbed.

Another occasional cause of aseptic inflammation at the site of a mechanical injury is the contamination of the tissues with such irritating body fluids as urine, bile, trypsin, or lipase. Thus, a small laceration of a biliary or pancreatic duct or of a ureter may lead to an inflammation response that is enormous in relation to the amount of primary tissue destruction.

The nature and sequence of the reactive changes that are elicited by mechanical disruption of cells does not differ significantly from that caused by other forms of injury and are discussed in detail in Chapter 3.

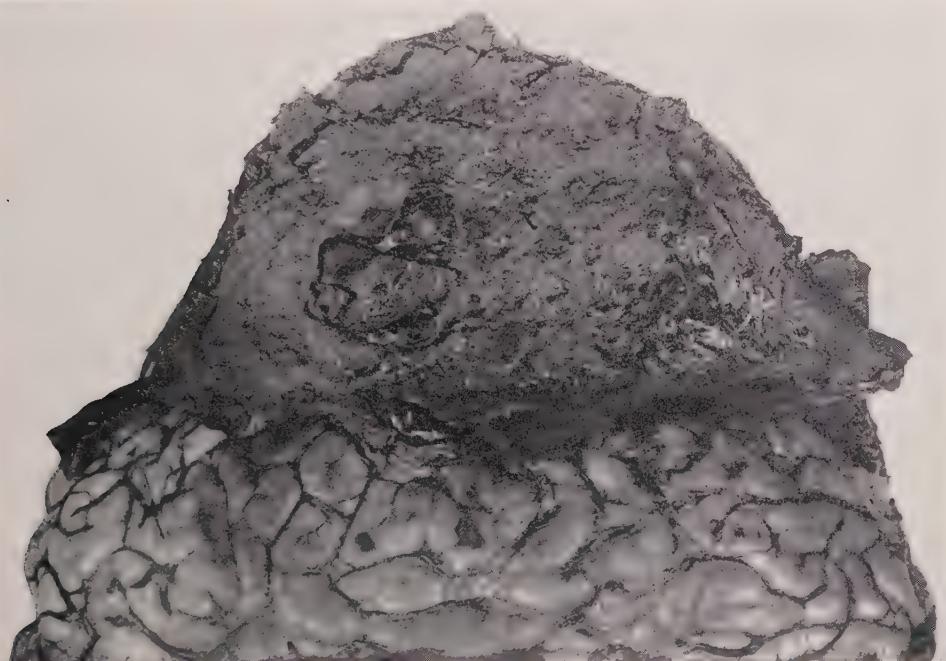


Fig. 90.—Subdural hematoma with compression of right cerebral hemisphere. The subject was an elderly alcoholic having a history of repeated accidentally incurred head injuries during the last year of life. Microscopic examination of hematoma disclosed evidence of repeated episodes of hemorrhage with formation of several membranes.

that the remains of mechanically disrupted cells are capable of disturbing their surviving neighbors. It also appears that different kinds of cells differ considerably in respect to the amount or nature of irritating substances that they are capable of liberating. Thus, a disruptive injury of skeletal muscle invokes a much greater inflammatory reaction than is elicited by a comparable injury of fat or fibrous connective tissue.

Another important factor in determining the severity of the inflammatory reaction to mechanical injury is the extent to which the trauma may interfere locally with the circulation of blood. Thus a small primary injury in respect

Although dilatation of small blood vessels and margination and emigration of leukocytes may be seen at the site of a wound as early as thirty minutes after it has been incurred, the failure to observe such changes does not constitute proof of a shorter posttraumatic interval. Such an inflammatory reaction may be delayed or suppressed by local or generalized circulatory failure. In the case of blunt impacts considerable hemorrhage may be caused by damage to capillary

walls with minimal concomitant injury to extravascular tissue. In such an event, the inflammatory reaction to the trauma may be negligible.

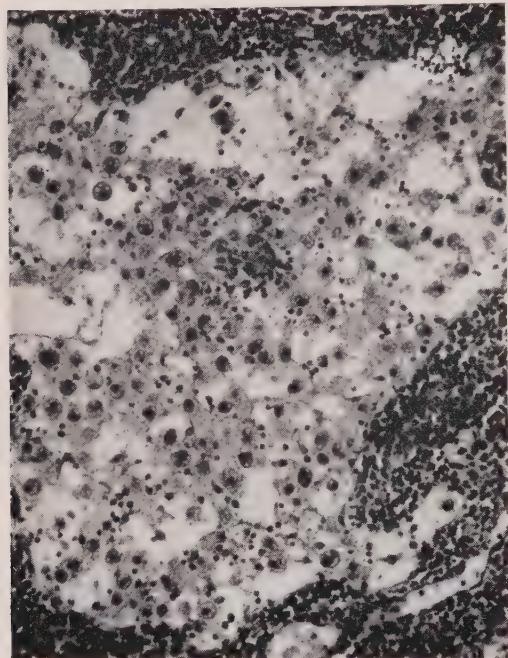


Fig. 91.—Aseptic inflammation. Reaction of reticular cells and fixed macrophages in regional lymph node to toxic products derived from mechanically disrupted tissue. Forty-eight hours after injury. ($\times 100$.)

Other Local Circulatory Disturbances.—Attention has already been directed to the circulatory disturbances that may be induced by an expanding hematoma and to those that occur incident to the vascular participation in the phenomenon of inflammation. Various other factors may contribute to local disturbances in circulation following the receipt of a mechanical injury.

One of these is the occurrence of regional vascular spasm of sufficient extent and severity that the original injury is enlarged by the occurrence of secondary ischemic necrosis. Generalized ischemia of an extremity may result from reactive spasm of large and apparently unwounded arteries following the incurrence of an injury whose disruptive effects were local. Nonthrombotic ischemia apparently due to vasospasm is sometimes responsible for the progressive enlargement by in-

farction of relatively small primary injuries of the brain or kidney.

Similar enlargement of the original scope of injury may result from the propagation of a thrombus from the site of a disruptive vascular injury or from stasis and thrombosis caused by post-traumatic vascular compression by edema or interstitial hemorrhage. In the case of disabling injuries the muscular inactivity imposed by disability is an additional cause of stasis and may be responsible for thrombosis in the region of injury or elsewhere.

It should be borne in mind that intravascular stasis may be sufficient to cause thrombosis independently of preceding injury to the affected vessel. Although it is unlikely that thrombosis will occur in a normal vessel, it is equally true that the lining of a vessel does not remain normal for long after the blood within it has ceased to flow. Degeneration of the lining endothelium and edema of the intima occur concomitantly with stasis. Platelets adhere to the damaged lining. In the case of larger vessels, clot formation begins at the periphery of the stream and progresses toward the center until the obstruction is complete. In the case of small vessels, much or most of the fluid elements of the blood diffuse through the vascular wall, leaving the distended lumen occluded by a solid sausagelike mass of closely packed erythrocytes.

Mechanical Injury and Local Infection.—Any injury that disturbs the continuity of that protective and especially adapted layer of cells that stands between the organism and its external environment, whether it be the integument or the mucous membrane lining an internal passage, may create a portal of entry for infection. The infective agent may be carried into the tissues on the surface of the instrument that was responsible for the wound or may subsequently gain access to the tissues because of the existence of a wound.

Under nonsurgical conditions any instrument responsible for the production of a mechanical injury is likely to be contaminated with pathogenic organisms. The most important source of such contamination is soil, and *Clostridium tetani* and *welchii* are among the more important pathogenic inhabitants of soil. Strepto-

cocci, staphylococci, *Proteus vulgaris*, and *Escherichia coli* are commonly present on the skin. Pathogenic organisms that may be present on the surface of mucous membranes of the body include streptococci, pneumococci, meningococci, *Hemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Clostridium welchii*.

The creation of an external portal of entry is by no means the only mechanism by which mechanical violence may render the site of an injury vulnerable to infection. Even though primary wound infection does not take place, a locus of diminished resistance may be established. Delayed infection of the injured tissue by way of the blood stream may occur because of the creation locally of conditions favorable to bacterial growth.

SYSTEMIC EFFECTS OF MECHANICAL INJURY

Almost immediately, incapacitating systemic anoxia may be the direct consequence of an injury if its primary effect is such as to interfere with respiration or systemic circulation. Certain types of disruptive injury of the brain or heart may thus be the direct and immediate cause of fatal systemic disturbance. It should not be concluded, however, that wounds of these structures are invariably fatal. So long as the brain stem escapes damage, extensive and disruptive cerebral injury may not only be survived but may not even cause loss of consciousness. Through-and-through stab or bullet wounds of the heart are sometimes survived and even those that eventually cause death may not be immediately incapacitating.

It is a fact, however, that even though the function of the damaged tissue is not normally concerned with such basic physiologic processes as respiration, circulation, nutrition, or elimination, such an injury may be responsible for systemic disturbances by any one of several mechanisms.

Although the cause and nature of such disturbances will be described in detail in various other sections of this book, it will not be unduly repetitive to bring them to the reader's attention at this time.

Primary Shock.—A mechanical injury to any part of the body may elicit a reflex vasodilata-

tion and a fall in blood pressure of sufficient severity to cause collapse, loss of consciousness, and in some instances death. This type of posttraumatic circulatory disturbance constitutes the syndrome of primary or neurogenic shock. The investigations of Weiss and Baker³ have shown not only that different individuals vary greatly in respect to their susceptibility to this type of reflex vascular disturbance, but also that some parts of the body are much more likely than others to give rise to such reflexes. Thus, pressure on the carotid sinuses, a blow to the epigastrium or a testicle, puncture of the pleura, or dilatation of the rectum may lead to sufficient fall in blood pressure to result in unconsciousness and, occasionally, in death. It is likely that certain deaths attributed to status thymicolumphanticus are actually instances of primary shock in persons abnormally susceptible to reflex circulatory disturbance.

That the fall in blood pressure in such circumstances is due to pooling of blood in dilated vessels and not to loss of blood volume due to the escape of plasma into the interstitial spaces is indicated by the recent investigations of Phemister and his associates.⁴ (See also discussion on page 100.)

Systemic Effects of Hemorrhage.—The initial systemic effect of loss of blood is mechanical and due to diminution in blood volume. The initial compensating reaction to the shrinking blood volume is reflex vasoconstriction. Secondly there is mobilization of fluid reserves and dilution. The reserves of blood cells in the bone marrow and spleen are such that a considerable blood loss may be sustained without significant change in the hematocrit. If bleeding continues, however, compensation fails, the volume of circulating blood decreases, and if the pressure falls below a certain critical level the vaso-motor centers become anoxic and the resulting vasodilatation leads to rapid circulatory collapse and death.⁵ The amount of hemorrhage necessary to produce circulatory collapse is subject to considerable individual variation. If vascular tone is already impaired by primary shock, a relatively small hemorrhage may be fatal. In the dog the continuation of bleeding beyond the point at which the blood loss is 3 per cent of the body weight is said to result in a rapid decline in blood pressure and circulatory collapse.⁶

The histologic changes elicited in hemopoietic tissue as a result of blood loss will be described in another place. In cases of death from acute massive hemorrhage the most significant post-mortem changes are gross rather than microscopic and consist of generalized pallor of tissue, collapse of the great veins and a flabby shrunken gray spleen (see also page 96).

Secondary Shock.—Two types of posttraumatic circulatory failure due to a diminution in effective blood volume have already been described. One was caused by hemorrhage and the other was neurogenic and due to reflex peripheral vascular collapse.

Another type of posttraumatic circulatory failure due in part or entirely to diminution in blood volume by loss of plasma is responsible for the syndrome of secondary shock. There is usually an interval of hours between the in-

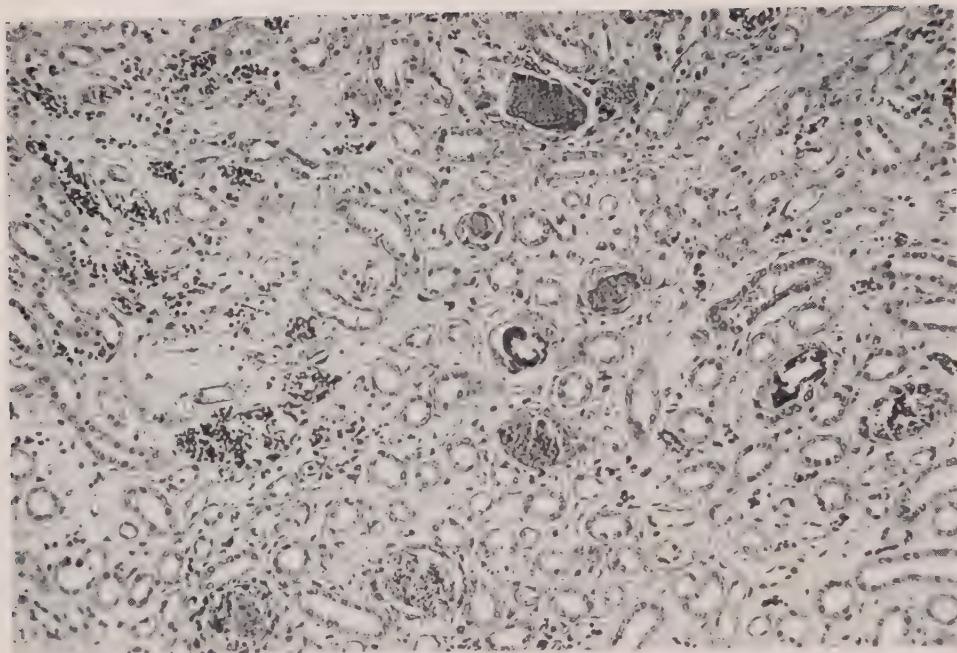


Fig. 92.—Renal changes in crush syndrome. Obstructive pigmented casts in lower segments of nephrons with tubular epithelial degeneration and interstitial edema. Posttraumatic anuria and azotemia with death on sixth day. ($\times 100$.)

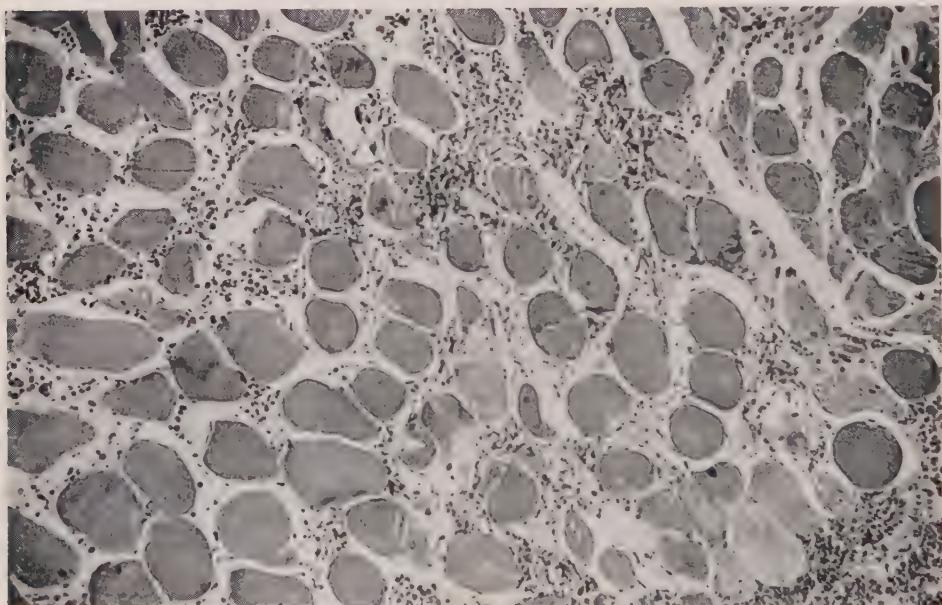


Fig. 93.—Ischemic necrosis of gastrocnemius muscle six days after a crushing injury. The necrotic muscle fibers are swollen, have lost their nuclei, and appear homogeneous rather than fibrillar. There is marked interstitial edema with sparse infiltration by extravasated erythrocytes. ($\times 140$.) See Fig. 92, showing renal changes in same individual.

jury and the onset of secondary shock, and although secondary shock may follow and merge with the signs and symptoms of primary shock and may be complicated and contributed to by hemorrhage, it may occur independently of either.

A more detailed discussion of the pathogenesis and pathologic characteristics of secondary shock will be found in Chapter 5.

Crush Syndrome.—This variant of the usual syndrome of secondary shock in which renal failure is an outstanding feature may occur in persons who have sustained extensive crushing injuries of the extremities and has been encountered with particular frequency among air-raid casualties.⁷ Signs of secondary shock are likely to appear during the first or second day after injury and for several days the diminishing urine contains pigment and pigmented casts. Azotemia develops as the urinary output decreases and death from uremia often occurs within the week.

Postmortem examination discloses the damaged muscles to be swollen, friable, opaque, and pale. Necrosis may or may not be present, depending on the duration and severity of the compressive ischemia. Chemical examination of muscle damaged in this manner may show an almost complete loss of pigment. The renal changes include tubular epithelial degeneration which is particularly pronounced in the lower portions of nephrons and obstructive pigmented casts which are most numerous in the collecting tubules. According to Lucké⁸ the impairment of renal function probably represents the combined effects of tubular degeneration, tubular obstruction, and low glomerular filtration pressure (see also page 588). Oliver and his associates^{7a} have produced the lesion in experimental animals by combining peripheral trauma with an episode of renal ischemia.

General Adaptation Syndrome.—The frequent occurrence of a posttraumatic neuroendocrine disturbance in the form of an evanescent hyperglycemia has long been recognized. That the neuroendocrine reaction to an injury may be such as to modify significantly its total effect on the organism was not fully appreciated prior to the investigations of Selye.⁹

It has since been shown that a wide variety of damaging stimuli may cause the pituitary to discharge an excessive amount of corticotrophic hormone which in turn leads to an outpouring of cortical hormone from the adrenals. Pathologic evidence of this effect on the adrenals may be recognized within the first few days after an injury by partial or complete depletion of lipid from the cortical cells. That the reaction is part of a defense mechanism can be inferred from the fact that cortical hormone may cause a rapid release of antibodies from lymphoid tissue. The pathologic evidence of this effect is manifested by the rapid involution of thymus and lymphoid tissue due to the disintegration of lymphocytes *in situ*. Continued stimulation of the adrenals leads to degenerative changes in the cortex, and in animals the excessive and prolonged secretion of cortical hormone is thought to be responsible for a variety of alterative changes throughout the vascular system.

Posttraumatic Embolism.—Any one of several types of emboli may gain access to the circulation as a result of mechanical disruption of tissue.

If adipose tissue is bruised, lacerated, or incised, fat droplets may enter the disrupted veins and be carried to the lungs, where, if they are sufficiently numerous, they may occlude so many of the pulmonary capillaries as to cause death. One of the most common causes of fat embolism is fracture of a long bone. If a significant degree of clinical or functional disturbance results from pulmonary fat embolism following an injury to extraskeletal adipose tissue, it usually does so within twenty-four hours. This is not true, however, in the case of pulmonary fat embolism following fractures of long bones. Fatal fat embolism following a fracture of a long bone may be delayed for as long as several weeks after the incurrence of the injury.

Pulmonary fat embolism occurs much more frequently than is commonly suspected. A surprisingly large amount of fat may be present in the pulmonary capillaries without causing a significant degree of functional disturbance. The presence of pulmonary fat embolism may be readily recognized by appropriately stained frozen sections. If a significant degree of capillary occlusion has occurred, there will be extravasated erythrocytes and there may be free fat droplets in the pulmonary alveoli. If the amount of fat in circulation is large a considerable amount of it may pass through the pulmonary capillaries and lodge in the terminal vessels of the central nervous system to cause death by cerebral rather than pulmonary embolism or by a combination of both (see also page 116).

A detached blood clot represents another type of embolism frequently caused by mechanical injury. Venous thrombosis may occur as a direct result of trauma to a vein or of stasis caused by edema or by muscular inactivity. Thus, the thrombus may form at the site of injury or at some remote place in the body. The spontaneous detachment of such a thrombus frequently results in pulmonary embolism.

A third type of embolism that may be caused by mechanical injury results from the entrance of air into the circulating

blood. The most common portal of entry for fatal air embolism are the dilated veins of the gravid uterus. Large amounts of air may be sucked into the uterine veins during an attempt to empty the uterus by instrumentation or by irrigation. Air embolism may result from tubal insufflation, from the insufflation of a nongravid uterus, from the injection of air into the peritoneal cavity, or from incision or laceration of veins anywhere in the body. Small amounts of air may enter the veins and be carried to the lungs without causing significant disturbance. If the amount of air is large, the right side of the heart and the pulmonary arteries become occluded by foam, and death results from acute circulatory failure. As a result of penetrating injuries of the lungs, air may be carried to the left side of the heart and thence to the systemic circulation to cause death from cerebral or coronary air embolism (see also page 116).

of change. The circumstances in which man may be exposed to extreme changes in atmospheric pressure range between an increase of several atmospheres, such as may take place in a caisson, to a decrease to a fraction of an atmosphere, such as occurs at a stratospheric altitude.

DIRECTION AND MAGNITUDE OF CHANGE.—The human organism tolerates an increase in atmospheric pressure better than it does a decrease of equal magnitude. Thus the atmospheric pressure of man's environment can be tripled without harm and yet a lowering of the pressure by as little as 50 per cent incident to an elevation to an altitude of 20,000 feet results in severe systemic anoxia and may cause death.

RATE OF CHANGE.—The rate at which a change in atmospheric pressure takes place, and more particularly the rate at which it is decreased, is an exceedingly important factor in injury production.

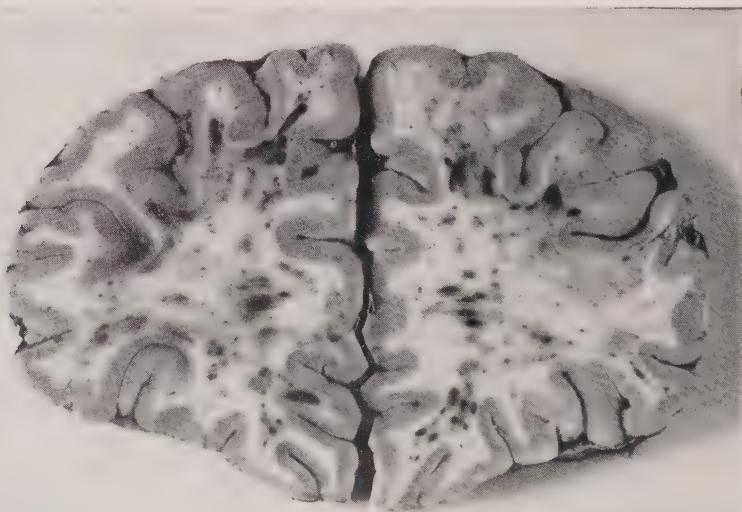


Fig. 94.—Cerebral fat embolism. The focal hemorrhages are larger than those ordinarily encountered.

INJURIES CAUSED BY CHANGES IN ATMOSPHERIC PRESSURE

General Considerations.—The three characteristics of an episode of abnormal atmospheric pressure that determine its injurious effects on man are (1) the direction and magnitude of change, (2) the rate of change, and (3) the duration

Unless atmospheric pressure is lowered slowly, whether it be from a high to a normal level or from a normal to a low level, bubbles of nitrogen are likely to form in the blood as the change in tension releases the gas from solution.¹⁰ The gas bubbles thus released occlude capillaries and produce the syndrome of aeroembolism, also known as caisson disease, the

bends, the staggers, or the chokes. Because of the solubility of nitrogen in lipoids, obese persons have a larger reservoir of dissolved nitrogen than nonobese persons and are particularly likely to develop aeroembolism. If, prior to rapid decompression, enough oxygen is breathed to replace a substantial amount of the dissolved nitrogen, the danger from aeroembolism is substantially reduced.

Disability and death from aeroembolism may supervene within minutes or hours after the onset of decompression. Although the occlusive gaseous emboli are distributed generally throughout the circulating blood, it is in the white matter of the brain and spinal cord that they are most numerous. Foci of ischemic necrosis may become visible in the white matter if the acute phase of the syndrome is survived.

A collateral effect of a rapid drop in atmospheric pressure is the expansion of air in the paranasal sinuses and in the middle ears, leading to pain and occasionally to rupture of the eardrums.

The effects of a rapid increase in atmospheric pressure are far less injurious than those of decompression. The most important compression effect is the acute discomfort caused by the inward displacement of the eardrums (see aerotitis media, page 701).

Blast Injury.—The term "blast injury" designates the disruptive effects of the sudden changes in pressure that result from an explosion. If the force of the explosion is transmitted through the air, the term "air blast" is employed; if through water, "immersion blast," and if through more or less rigid structures, "solid blast."^{11, 12}

In the case of an air blast the compression tends to be unilateral and its principal effect is on the side of the body that faces the explosion. In the case of an immersion blast in which partially or completely immersed persons are exposed to an underwater explosion, the body is compressed from all sides and the injurious internal effects tend to be diffuse rather than localized. In the case of a solid blast the disruptive force of the explosion is transmitted to the body through those parts of it that are in contact with an agitated rigid structure such as the deck of a ship or the wall of an air-raid shelter.

In both air blast and immersion blast the injury is due to the establishment of sharp pressure gradients within the body. Differences in fixation, cohesion, compressibility, and inertia on the part of the various components of the body result in nonuniform response to the dis-

placing force and in widespread disruptive change. Thus, the walls or compartments of hollow viscera are particularly susceptible to blast injury. In the case of air blast, multiple lacerations of the lungs are commonly sustained with intra-alveolar bleeding, a prominent feature of the postmortem findings. In the case of immersion blast, ruptures of the intestines are common. Diffuse injuries of both the thoracic and the abdominal viscera may occur with either air or immersion blast and may be sustained with little or no external evidence of trauma.

It should be borne in mind that close proximity to either type of explosion may result in virtual destruction of the body by the extreme air or water turbulence induced by the blast. Flying missiles may add an infinite variety of wounds to those induced by turbulence and compression. In the case of air blast the victim may be burned, may be asphyxiated by irrespirable combustion products, or may sustain secondary injuries as a result of being knocked down or of being crushed by falling buildings or debris. The violent motion imparted to the deck of a ship or to the floor of a building by an explosion may cause disruptive impacts against the feet of standing personnel.

DURATION OF CHANGE.—There is no evidence that prolonged exposure to high atmospheric pressure is injurious if decompression occurs slowly. Prolonged exposure to low atmospheric pressure represents a protracted period of chronic anoxia and may lead to the syndrome of mountain sickness which is characterized by headache, vertigo, epistaxis, and diminished capacity for work. As acclimatization to the diminished oxygen tension occurs, there is polycythemia, increase in blood volume and hemoglobin, hyperplasia of the bone marrow, and sometimes osteoarthropathy of the fingers and toes.¹³

INJURIES BY SOUND WAVES

The vibrations of audible sound rarely produce morphologically recognized injury and then only when the exposure is of unusual intensity and duration. Boilermakers and others engaged in similarly noisy occupations may become deaf to tones in the same range of pitch as those to which they have been exposed and are said to develop degenerative changes in the basilar membrane of the cochlea.

Supersonic vibrations are those that are above the limits of hearing of the human ear and have greater capacity for the production of biologic reactions than do sonic exposures of lower frequency.

The precise mechanism by which supersonic vibrations cause some of the bizarre central nervous system disturbances that have been observed in human subjects is not known. In experimental animals and lower forms of life there appear to be at least three mechanisms by

which supersonic radiation may cause injury. One is by physical disintegration of the intracellular gel, with the formation of submicroscopic gas-filled cavities, due to the tremendous pressure differences between the rapidly recurring crests and troughs of the sound waves.¹⁴ Another is by the induction of hyperthermia. Temperature increases by as much as 9° C. in liver and 25° C. in fat have been recorded after thirty-second exposures to supersonic radiation.¹⁵ A third mechanism of supersonic injury is the induction of chemical changes in the exposed cells.

The injurious effects of supersonic energy on mammals have been studied by Lynn and Putnam¹⁶ who produced destructive cerebral and spinal cord lesions in cats, dogs, and monkeys without concomitant damage to the skull or vertebral column. Edema, hyperemia, and degeneration of both nerve and glial cells was observed. Healing was accompanied by diffuse gliosis.

INJURIES BY HEAT AND COLD

General Considerations.—Despite man's ability to survive wide variations in environmental temperature, his internal temperature must be maintained within a narrow range if thermal injury is to be avoided. Thus, cellular injury or death occurs if tissue temperature is maintained at a level more than 5° C. above, or more than 15° C. below, that which is normal for the blood. The severity of injury caused at any given temperature tends to be proportional to the duration of the hypo- or hyperthermic episode. The somatic function of circulation is more susceptible to irreversible disturbance by dysthermia than are the individual cells of the body, and hence somatic death may result from a systemic alteration in temperature that would not cause cellular death if it were localized.

The principal site of heat loss during exposure to a cold environment or of heat gain during exposure to a hot environment is the skin. The respiratory membranes are rarely injured either by heat or by cold and then only when the alteration of air temperature is so extreme that the skin is burned or frozen.^{17, 18}

Local Hypothermia.—Chilling of tissue retards the metabolic activity of the cells and may cause irreversible cellular change due to intracellular ice formation. This is not to imply, however, that hypothermic injury is dependent on the occurrence of congelation. The most important injurious effects of chilling are the alternative changes that occur in the walls

and contents of the small blood vessels. A brief period of severe or a protracted period of mild tissue hypothermia may injure capillary endothelium sufficiently to cause transudation of fluid and edema. Superficially such edema may lead to extensive vesication. Different individuals vary greatly in respect to their threshold for edema formation incident to chilling.

If chilling is rapid and severe, the tissue may be rendered ischemic so quickly that evidence of vascular injury does not become apparent until the temperature rises and circulation is re-established. Intense hyperemia is usually the immediate response to restitution of circulation after hypothermia. The hyperemia is followed by edema as soon as sufficient time has elapsed for plasma to diffuse through the walls of the injured vessels.

During a protracted episode of nonfreezing hypothermia such as that which causes "immersion" or "trench" foot, or following a brief episode of freezing hypothermia such as causes frostbite, the local vascular injury may be so severe that the capillaries and even the larger vessels become plugged by tightly packed masses of erythrocytes. The nature and severity of the subsequent changes are determined by the extent and permanence of the ensuing ischemia. If the vascular occlusion is extensive, complete infarction in the form of moist or dry "gangrene" takes place. If the necrotic tissue becomes moist and dark colored, it can be inferred that infarction was preceded or accompanied by some degree of vascular patency. If the necrotic tissue becomes dry and mummified, it can be inferred that vascular occlusion was complete from the beginning.

Extensive studies of the pathologic changes of protracted nonfreezing hypothermia seen in "trench" or "immersion" foot indicate that most if not all of the residual injury can be attributed to the ischemia that results from the vascular occlusion. That certain direct effects of low temperature on lipid-rich tissue may contribute to the total injury cannot be excluded. Atrophic and degenerative changes are seen in the epidermis, sweat glands, nerves, subcutaneous fat, and skeletal muscle with proliferation of fibrous connective tissue in all situations.¹⁹

Systemic Hypothermia.—If the area exposed to cold is relatively small, a severe local injury may be sustained without significant lowering of the blood temperature. If the area of exposure is large, the body temperature may be lowered sufficiently to cause death from circulatory failure even though no local injury has been sustained. Circulation fails when the temperature of the blood is reduced to the vicinity of 20° C.²⁰ Immersion in cold water or exposure to a rapidly moving current of cold air may lower the body temperature to a fatal level in a remarkably short period of time. There are no histologic or anatomic changes that can be regarded as pathognomonic of death due to systemic hypothermia. Post-mortem examination of persons who have died from exposure to cold may disclose nothing more than a moderate degree of right heart dilatation and pulmonary edema.

Local Hyperthermia.—Man is far more susceptible to injury by an increase than he is by a decrease in tissue temperature.

An elevation of tissue temperature by even a few degrees above that which is normal for the blood is injurious. At any given temperature the occurrence or non-occurrence of irreversible injury is determined by the duration of the hyperthermic episode. During episodes of low intensity (40 to 45° C.) the rate of injury exceeds that of recovery by so narrow a margin that many hours are required before irreversible changes have occurred. The higher the temperature the shorter the time required to cause cell death.^{21, 22}

Since the rise in tissue temperature incident to exposing the surface of the skin to excessive heat is greatest at the surface and becomes progressively less as the distance from the surface is increased, it is apparent that any given burn will include a wide range of thermal effects. The cytoplasm of thermally injured cells becomes at first granular and later homogeneously coagulated. The collagen tends to lose its fibrillar character and to take on the appearance of a dense and more or less homogeneous gel. That there is a fall in the pH of the thermally denatured cells is indicated by their increased affinity for basic stains.

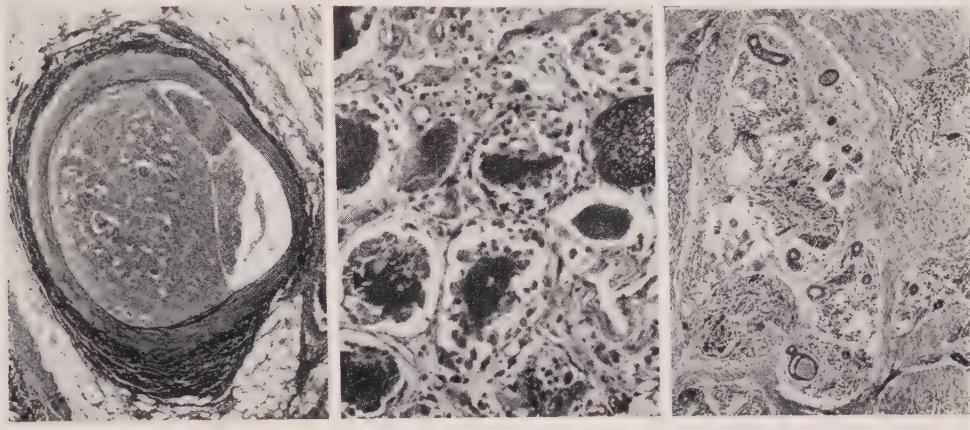


Fig. 95.—Characteristic pathologic sequelae of hypothermic injury. *A*, Trench foot. Agglutinative thrombus in artery ($\times 75$). *B*, Trench foot. Degeneration, necrosis, and phagocytosis of muscle fibers ($\times 220$). *C*, Frostbite. Dermal fibrosis with atrophy of sweat glands ($\times 100$). (Reproduced by courtesy of the Armed Forces Institute of Pathology.)

The earliest evidence of hyperthermic injury is functional rather than structural. Capillaries and small blood vessels become dilated as the tissue temperature is raised, the permeability of the capillary walls is increased and the fluid components of the blood leave the vessel and enter the interstitial spaces with resulting edema. When thermal edema occurs in the superficial portion of the skin, the fluid may collect beneath the epidermis, with resulting vesiculation.

The earliest cytological evidence of hyperthermic injury is a redistribution of the fluid and solid components of the nuclei, followed by nuclear swelling due to the imbibition of fluid, rupture of the nuclear membranes, and finally pyknosis.

Cutaneous burns may be designated as first, second, or third degree. First-degree burns are manifested by erythema without significant alteration of the epidermis. Second-degree burns are those in which the epidermis has been destroyed without significant irreversible injury to the dermis. Such burns are characteristically vesicated but, because of little or no permanent damage to the dermis, healing by epithelial regeneration is ordinarily prompt. Third-degree burns are those in which there has been sufficient damage to the dermis as to interfere with epithelial regeneration. The irreversibly injured dermis must be disposed of before a new layer of epithelium can be regenerated. The organization and repair of the damaged dermis is accomplished by growth of new fibrous connective tissue and often results in extensive scar formation.

Vascular reaction with hyperemia and edema is inevitable if the tissue hyperthermia has been sufficient to be injurious and frequently occurs before the duration or the intensity of

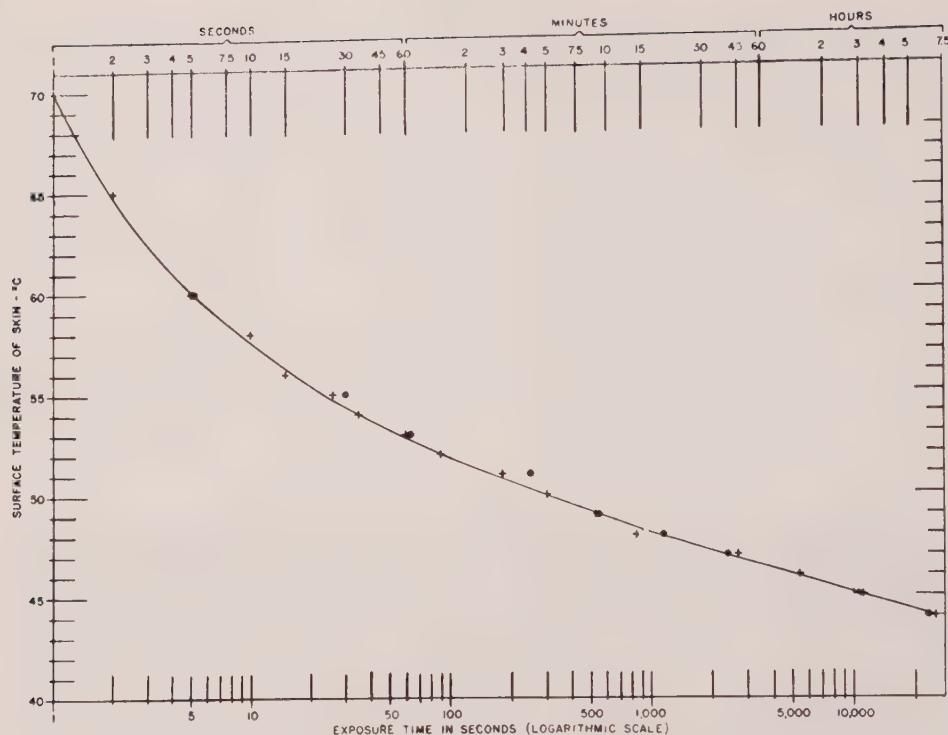


Fig. 96.—Cutaneous burning. The curve represents the time-temperature threshold for the production of transepidermal necrosis. Exposures that are significantly subthreshold can be tolerated with little or no irreversible injury. Exposures that are significantly suprathreshold destroy the epidermis and cause varying degrees of irreversible dermal injury. (From experimental data by Moritz and Henriques.)



Fig. 97.—Experimentally produced second-degree burn of human skin caused by maintaining the surface temperature at 45°C. for three hours. Transepidermal necrosis with vesication. Irreversible dermal injury was minimal and epidermal regeneration was complete in ten days.

the exposure has been great enough to cause any other perceptible evidence of injury.

In the case of exposure to intense heat the superficial vessels may become so rapidly fixed in a state of contraction that neither edema nor hyperemia is visible from the surface. In such an event the reactive vascular changes will occur at a lower level, but with no less severity. One of the most important systemic effects of extensive cutaneous burning is secondary shock brought on by hemoconcentration due to loss of plasma at the site of injury.

Thermally denatured tissue elicits an aseptic inflammatory reaction, represents a foreign body, and must undergo lysis and organization or be sloughed off as a sequestrum. Prior to organization or sequestration it provides a favorable medium for bacterial growth and predisposes the adjacent tissue to infection. Collection of lymph flowing from burned tissue has provided evidence that systemic injury may result from the release of proteolytic enzymes by the damaged cells.²³

Systemic Disturbances Caused by Cutaneous Burns.—Burning of the surface of the body may result in a wide variety of secondary disturbances. Such an injury may precipitate the development of primary or neurogenic shock with

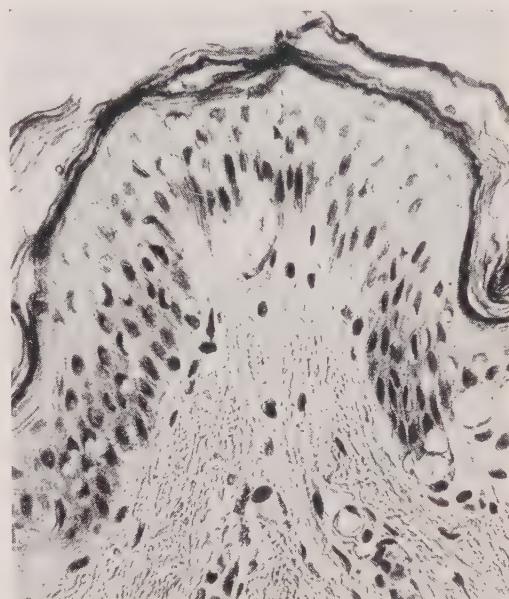
rapid peripheral circulatory collapse leading either to syncope or to death. The progressive loss of plasma from the burned surface or into the damaged tissue beneath it may result in hemoconcentration and secondary shock. The extent to which secondary shock or other systemic disturbances may be contributed to by the liberation of poisonous substances from the burned tissue is not known. It is a reasonable inference that the hemoconcentration, low blood pressure, and systemic anoxia of secondary shock predispose not only to phlebothrombosis, particularly in immobilized extremities, but also to occurrence of the degenerative changes that are so commonly observed in the kidneys, liver, and adrenals of burned persons.

Although the precise cause of the ulcers that sometimes develop in the proximal portion of the small intestine of severely burned persons is not known, local mesenteric thrombosis and mucosal infarction would appear to constitute a plausible explanation. The degenerative changes frequently observed in the cortical cells of the adrenals of persons who have died several days after severe cutaneous burning may be due in part to the participation of that organ in the adaptation reaction.⁹ Hepatic necrosis, formerly believed to be a complication of cutaneous burning, occurs almost exclusively in persons whose burns have been treated with tannic acid. It is now believed to be due to the treatment rather than to the burn.^{23a}

Erythrocytes break down rapidly *in vitro* at temperatures over 50° C. and *in vivo*, at temperatures over 42.5° C.,^{23b} and intravascular hemolysis usually takes place if the hyperthermic episode has been of sufficient intensity or duration to destroy the epidermis. Free plasma hemoglobin is excreted rapidly by the kidneys, where it may be precipitated in the lower segments of the nephrons to form obstructive casts similar to those which form as a result of a mismatched transfusion. The combined effect of the tubular lesions and the low glomerular filtration pressure results in a type of renal disturbance which Lucké has characterized as the "lower nephron syndrome"²⁸ (see page 588).

Systemic Hyperthermia.—The temperature of the body may be raised to an injurious level either by the inflow of heat from without or by its failure to eliminate the heat developed by metabolic processes. A general rise in the temperature of the circulating blood to a level higher than 42.5° C. leads to profound functional disturbances. These include (a) generalized vasodilatation with resulting reduction in

A.



B.

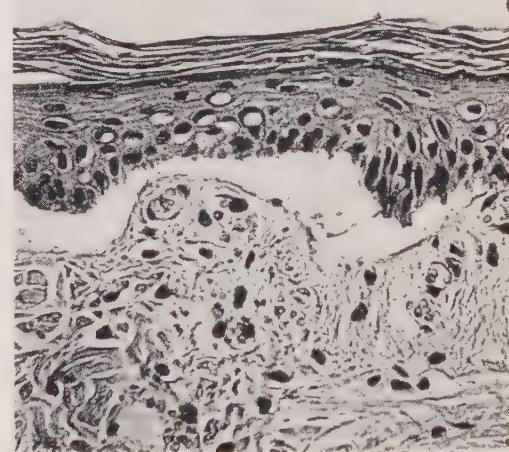


Fig. 98.—Cutaneous burns. In A, the burn is mild and although the epidermis is damaged it is not completely destroyed. Many of the nuclei are swollen and show eccentric displacement of chromatin. Minute vesicles have formed at the junction of dermis and epidermis. B, shows a second-degree burn. Vesication is complete. The entire thickness of the epidermis is necrotic and detached from the relatively uninjured dermis. ($\times 400$)

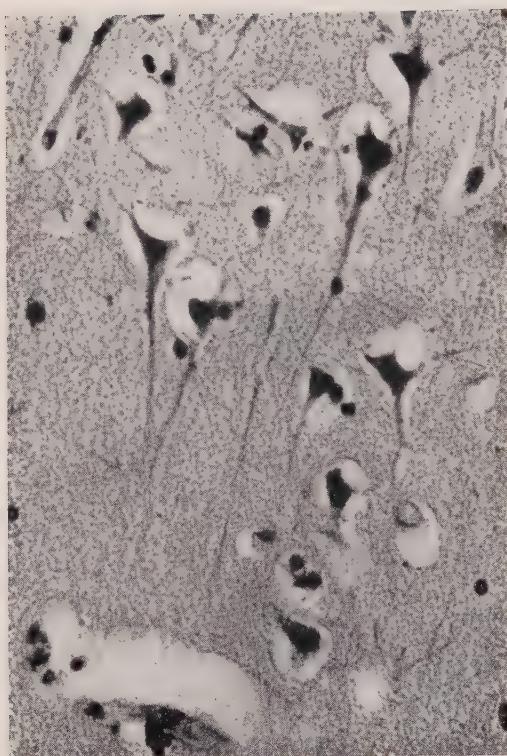


Fig. 99.—Early manifestations of hyperthermic injury (heatstroke) in cerebral cortex. Cells are pyknotic and hyperchromatic. Such degenerative changes may be followed by disintegration and disappearance of neurons and diffuse cortical gliosis. ($\times 450$) (Reproduced by courtesy of the Armed Forces Institute of Pathology.)

effective blood volume, (b) rapid pulse and dilatation of the heart with impairment of cardiac efficiency, and (c) stimulation of the respiratory centers manifested first by tachypnea and later by irregularity and finally suspension of respiratory activity.²⁴ It is difficult to determine which of these several physiologic effects of systemic hyperthermia may contribute most to somatic deterioration and death. It is of interest in this connection that a heart-lung preparation fails when the temperature of the perfusate reaches the vicinity of 42.5°C .

In the case of cutaneous exposures to conflagration temperatures, the internal temperature of the body may be raised by between 5 and 8°C . within a few minutes, with death occurring soon thereafter. In such instances the physiologic disturbances due to hyperthermia are augmented by rapid pooling of blood in the dilated vessels of the superficial tissue and in some instances by excessive elevation of plasma potassium due to the release of this ion from thermally damaged erythrocytes. Plasma potassium levels as high as 20 mEq/L have been observed in experimental animals within ten minutes after the onset of general cutaneous exposure to excessive heat. To attain such a rise of plasma potassium the dermal tempera-

ture must be brought to and maintained at a level considerably in excess of 50°C .

Delayed systemic disturbances due to systemic hyperthermia include widely distributed degenerative changes in the parenchymatous viscera and particularly in the brain. For a complete account of the delayed pathologic changes caused by systemic hyperthermia, the reader is referred to the extensive studies by Malamud, Haymaker, and Custer.²⁵

ELECTRICAL INJURY

General Considerations.—The occurrence of electrical injury requires that some part of the body be interposed between two conductors in such a manner as to complete an electrical circuit. Thus, a live wire may be touched with impunity so long as such a contact does not complete a circuit and result thereby in the flow of an electric current through the tissues.

The path of a current through the body tends to follow the most direct route between the sites of entrance and exit.²⁶ In flowing through the tissues an electric current may cause injury by any one or a combination of several effects. Cells may be destroyed directly by heat or electrolysis. The current may stimulate strong muscular contractions or it may inhibit the function of any vital centers or organs that lie in the path of its flow.

When the contacts are appropriate for the flow of current through the tissues, the occurrence and nature of the harmful effects will depend (1) on the kind of current, (2) on the amount of current, (3) on the path of the current, and (4) on the duration of the current flow.

An alternating current is more effective in the production of physiologic disturbances than is a direct current and some alternating frequencies are more disturbing than others. The 60 cycle alternating current commonly available for domestic and industrial use lies in the frequency range which is particularly disturbing to the respiratory centers of the brain and to the heart.

The amount of current that will flow through the body when it becomes part of a circuit is determined by the formula $C = \frac{V}{R}$ in which C is the current in amperes, V is potential in volts, and R is the resistance in ohms with which the body opposes the flow of the current. Thus, the higher the voltage or the lower the resistance, the greater will be the flow of current. The usual currents available for domestic use have a potential of either 110 or 220 volts.

There is considerable indirect evidence that an alternating current in excess of 0.1 ampere and at a potential of 40 volts or more flowing through the brain stem of man may cause fatal interruption of respiration and through the human heart may cause fatal interruption of circulation. It is a fact that with favorable contacts between the skin and the external conductors the resistance of the human body may be reduced to less than 1,000 ohms. It is apparent, then, that an ordinary domestic current of 110 volts may be adequate to cause death if two conditions are fulfilled, namely, that the

contacts are such that a flow of at least 0.1 ampere takes place and that either the brain stem or the heart lies in the path of the current. It is also apparent that the higher the voltage the more dangerous the current will be.

In general, the severity of the disturbance caused by the flow of a given amount of current between similar external contacts is proportional to its duration. Certainly the generation of heat bears a linear relationship to time. Physiologic disturbances that are evanescent following a momentary shock may be rendered irreversible by a longer period of electrical exposure.

Actually most of the resistance offered by the human body to an electrical current is that of the skin and the interface between skin and external conductor. Thus, electrothermal injuries are ordinarily limited to the skin and the immediately subjacent tissue.

Thin skin is less resistant to the flow of electricity than thick skin and moist skin offers less resistance than dry skin. Heavily calloused dry skin may provide a resistance-protection of several hundred thousand ohms. Because of this fact persons with calloused hands often handle with impunity live wires that would be exceedingly dangerous if they were brought



Fig. 100.—Extensive electrothermal injury of child's arm caused by prolonged contact with noninsulated segments of an extension cord carrying an alternating current of 110 volts.

Electrical Burns.—The amount and place of heat formation incident to the flow of a given amount of electricity through the body are determined by the resistance that the tissue offers to the current. The formula by which the heating effect of a current is ordinarily calculated is $H = \frac{C^2 R}{4.187}$ in which H is gram-calories per second, C is current in amperes, and R is resistance in ohms.

in contact with a less resistant portion of the body surface.

If the contact between the skin and an external conductor is large, the generation of heat in terms of calories per cm.² of surface per second may be too low to produce a burn and yet the amperage may be more than enough to paralyze respiration or circulation. On the other hand, if the skin contact is a small one such as may occur by touching the end of a

live wire, the amount of heat generated in a few cubic millimeters of epidermis may be sufficient to produce a burn even though the total amperage has been insufficient to cause a significant degree of physiologic disturbance. Other things being equal, the rate of heat production increases geometrically as the voltage is raised.

Electrothermal burns have no consistent gross or microscopic characteristics by which they may be distinguished from other hyperthermic injuries. Arcing of the current may produce pitlike defects on the surface of hair or epidermis that are rarely, if ever, produced by other forms of heat. Metallic constituents of the external conductor may be deposited in or on the surface of an electrical burn and their presence may help to establish the kind of an electrode with which the skin was in contact. In the case of alternating current, such metallic deposits may be present at both sites of contact. With direct current, the deposits will occur only at the site of contact with the negative electrode.

a large electrothermal injury of the skin unless the contact is maintained for a considerable period of time.

Other Manifestations of Electrical Injury.

—Apart from injuries due to heat production and the explosive effects of currents of extremely high voltage there are no tissue changes that can be regarded as pathognomonic of electricity. Attention has already been directed to the fact that an electrical current flowing through the brain stem may cause death by inhibition of the respiratory centers and that electricity flowing through the heart may cause death by central circulatory failure. In neither circumstance does the passage of the current result in characteristic gross or microscopic alterations of the internal tissues. In both circumstances somatic death is likely to be preceded by a brief period of intense systemic anoxemia which may lead to the occurrence of petechiae in the serous membranes and in the central nervous system.



Fig. 101.—Electrothermal burn. Margin of severe (third-degree) burn, showing condensation coagulation, and intense basophilia of both epidermis and dermis. The abrupt transition from normal skin at right to transcutaneous necrosis at left would be most unusual in a thermal injury produced by means other than electricity. ($\times 100$.)

Electrothermal injuries should not be confused with the burns caused by contact with an object that has been rendered hot by a short circuit. If a short circuit occurs through a metallic conductor the flow of current through it may be so great that even with a potential of 110 volts its temperature is raised almost immediately to the melting point. Contact with such a superheated conductor will cause severe and instantaneous burning even though no electricity flows through the skin. When a current of 110 volts flows through the skin, the resistance is ordinarily so great that there is insufficient amperage for rapid elaboration of heat. Rarely does a current of 110 volts produce

References

1. Ham, G. C.: War. Med. 3: 30, 1943 (effects of centrifugal acceleration).
2. Moritz, A. R., and Dutra, F. R.: Arch. Path. 38: 339, 1944 (gunfire injury).
3. Weiss, S., and Baker, J. P.: Medicine 12: 297, 1933 (carotid sinus reflex).
4. Phemister, D. B., Laestar, C. H., Eichelberger, L., and Schachter, R. J.: Ann. Surg. 119: 26, 1944 (vasodepressor nerve impulses in causation of shock).
5. Cannon, W. B.: Am. Heart J. 14: 383, 1937 (factors affecting vascular tone).
6. Blalock, A.: Proc. Inst. Med. Chicago 9: 405, 1933 (acute circulatory failure in shock and hemorrhage).
7. Bywaters, E. G. L.: J. A. M. A. 124: 1103, 1944 (ischemic muscle necrosis).

- 7a. Oliver, J., MacDowell, M., and Tracy, A.: *J. Clin. Investigation* **30**: 1307, 1951 (lower nephron nephrosis).
8. Lucké, B.: *Mil. Surgeon* **99**: 371, 1946 (lower nephron nephrosis).
9. Selye, H.: *J. Clin. Endocrinol.* **6**: 2, 1946 (adaptation syndrome).
10. Thorne, L. J.: *J. A. M. A.* **117**: 585, 1941 (caisson disease).
11. Cohen, H., and Biskind, G. R.: *Arch. Path.* **42**: 12, 1946 (atmospheric blast injury).
12. Barr, J. S., Draeger, R. H., and Sager, W. W.: *Mil. Surgeon* **98**: 1, 1946 (solid blast injury).
13. Monge, C.: *Physiol. Rev.* **23**: 166, 1943 (chronic mountain sickness).
14. Schmitt, F. O., and Uhlenmeter, B.: *Proc. Soc. Exper. Biol. & Med.* **27**: 626, 1930 (Ultrasonic radiation injury).
15. Heidemann, E.: *Grundlagen und Ergebnisse der Ultraschallforschung*, Berlin, 1939, W. de Gruyter (ultrasonic radiation injury).
16. Lynn, J. G., and Putnam, T. H.: *Am. J. Path.* **20**: 637, 1944 (cerebral injury by focal ultrasound).
17. Moritz, A. R., and Weisiger, J. R.: *Arch. Int. Med.* **75**: 233, 1945 (effects of cold on respiratory tissues).
18. Moritz, A. R., Henriques, F. C., and McLean, R.: *Am. J. Path.* **21**: 311, 1945 (effect of heat on respiratory tissues).
19. Friedman, N. B.: *Am. J. Clin. Path.* **16**: 634, 1946 (reactions of tissue to cold).
20. Talbott, J. H.: *New England J. Med.* **224**: 281, 1941 (effects of hypothermia).
21. Moritz, A. R., and Henriques, F. C.: *Am. J. Path.* **23**: 695, 1947 (thermal injury).
22. Moritz, A. R.: *Am. J. Path.* **23**: 915, 1947 (thermal injury).
23. Zamecnik, P. C., Stephenson, M. L., and Cope, O.: *J. Biol. Chem.* **158**: 135, 1945 (thermal injury).
- 23a. Wells, D. B., Humphrey, H. D., and Coll, J. J.: *New England J. Med.* **226**: 629, 1942 (hepatic necrosis in burns).
- 23b. McLean, R., Moritz, A. R., and Roos, A.: *J. Clin. Investigation* **26**: 497, 1947 (thermal injury).
24. Moritz, A. R., Henriques, F. C., Dutra, F. R., and Weisiger, J. R.: *Arch. Path.* **43**: 466, 1947 (thermal injury).
25. Malamud, N., Haymaker, W., and Custer, R. P.: *Mil. Surgeon* **99**: 397, 1946 (heat stroke).
26. Weeks, A. W., and Alexander, L.: *J. Indust. Hyg.* **21**: 517, 1939 (electrical injury).

Chapter 7

CHEMICAL INJURY

WALTER W. JETTER

About 10,000 deaths from chemical injury take place annually in the United States. Although a wide variety of substances may cause chemical injury, statistics indicate that most cases of fatal poisoning in man are caused by a relatively few compounds. Among the more important of these are ethyl alcohol, carbon monoxide, anesthetic agents, barbiturates, and heavy metals. According to Gonzales, Vance, and Helpern,¹ approximately 55 per cent of all deaths due to chemical injury are accidental, 44 per cent are suicidal, while a considerably smaller number (less than 1 per cent) result from homicide.

To define the terms "poison" and "poisoning" is difficult. To be poisonous, a substance must exert its deleterious effect in small amounts (upper limit usually regarded to be 50 grams) and by its chemical action. Thus, finely ground glass, although injurious, is not a true poison since it produces injury by mechanical rather than by chemical action.

According to some, the toxic effect of equivalent doses of a poison should be regularly reproducible in the same species. On this basis, the various allergic manifestations which occasionally occur following the administration of simple chemical substances are excluded from the category of true poisoning. Taking into consideration all possible variants, Starkenstein, Rost, and Pohl² propose the following definition of noxious chemicals and their action, viz., "poisoning . . . a deleterious disturbance of function produced by physico-chemical materials, exogenous or endogenous, which are foreign to the body or tissue in respect to quality, amount or concentration."

MODE OF ACTION

General Toxicologic Action

Poisons may injure by local action at the portal of entry, by their action upon distant organs following absorption, or by a combination of both. The effects may be acute, delayed, or chronic. Some chemicals, such as the heavy metals, tend to damage tissue universally and are referred to as protoplasmic poisons. Other agents may, because of their selective action on certain tissues or their tendency to concentrate at certain sites, be nonuniformly injurious.

Fundamental Mechanism of Action

The fundamental mechanism by which poisoning occurs is by interference with the physical or chemical integrity of protoplasm.³ The

initiation of these disturbances may take place because of solution or chemical alteration of the cellular membrane with consequent changes in osmotic pressure relationships, because of changes in the electrical potential of cells, or because of a combination or direct reaction of any or all of the components of either cell or interstitial fluid with the noxious chemical agent.

Physiologic Effects

The physiologic effect of poisons may be reflected by myriad disturbances in a single or any combination of many functional systems. Thus, barbiturates and morphine specifically depress cells in the central nervous system, while strychnine incites them to hyperactivity. A state of acute anoxia may be initiated by carbon monoxide, which prevents the uptake of oxygen by hemoglobin or by cyanide which inhibits tissue oxidation. Other chemicals are deleterious because they compete for substances necessary to maintain life; for example, fluorides and oxalates remove calcium ions from solution, leading to a state of acute hypocalcemia. That the physiologic effect may at times become highly specialized is evidenced by the action of curare, which blocks transmission of nervous impulses, and by the profound cellular alteration that may be initiated following the local application of coal tars and other carcinogenic agents.

NATURE AND DISTRIBUTION OF PATHOLOGIC LESIONS

Concentration of chemicals in locations where they enter or leave the body is a factor of major importance in the production of pathologic lesions in gastrointestinal and respiratory tracts, skin, and kidneys. The effect may be accentuated in the first three of these situations since these organs may both excrete and receive the injurious chemical. Because of the vulnerability of alveolar capillaries, the entrance of many irritants into the pulmonary circulation, as well as direct inspiration of fumes, may give rise to rapidly fatal pulmonary edema. Another common effect of many chemicals is their hepatotoxic action. Concentration of the agent may take place because of the position of the liver in the portal circulation (in the case of poisoning by ingestion), the specific metabolism of the organ in its attempts at detoxification, or because of the excretion of the poison into the biliary system. Localization of injury in other organs not intimately associated with absorption, excretion, or metabolism of the poisonous chemical is less easily explained.

Upon the basis of their pathologic manifestations, most injurious chemicals may be divided into four groups:

1. No morphologic change can be attributed to the direct chemical action of the agent. Lesions, if present, are due to terminal systemic anoxia and are dependent upon the duration and severity of the agonal period of circulatory failure. Many poisons are classifiable in this group and particularly those which are rapidly fatal. They include the acute central nervous system depressants such as alcohols, ethers, and hydrocarbons; the chemical asphyxiants, such as carbon monoxide and cyanide; and many of the alkaloids. Many poisons which are potentially capable of producing recognizable structural alteration fall in this group when the dose is so great as to cause death before local lesions have had time to develop.

2. Systemic lesions are produced without evidence of injury at the portal of entry. Examples of this group are the acute hemolytic poisons such as arsine and nitrobenzene.

3. Injury at the portal of entry without remote or systemic evidence of direct injury. The corrosives and some of the gaseous irritants are the best examples of this group. The local pathologic lesion may be the factor immediately responsible for death (pulmonary edema following inhalation of gaseous irritant) or may cause acute vasomotor collapse.

4. Both local and systemic evidence of injury. The outstanding group of poisons which cause both local and systemic injury are the heavy metals, although numerous other chemicals may be included in this category.

CLASSIFICATION OF POISONS

For the purposes of discussing individual effect of poisons the following classification will be employed. In so far as possible, the classification follows physical and chemical properties; the main purpose, however, is to group compounds having similar toxicological and pathologic effects.

1. Corrosives—inorganic and organic.
2. Gases—irritants, chemical asphyxiants, systemic intoxicants, "war gases."
3. Metals.
4. Organic compounds—solvents, nitro and amino aromatic compounds, hypnotics and analgesics, alkaloids and glucosides, essential oils, miscellaneous.

Corrosives

Destroying protoplasm at point of contact, there are many substances that may be classified as corrosives. Many possess systemic toxicity, thus a very heterogeneous number of compounds are classifiable in the corrosive group. Inclusion of one and exclusion of another is arbitrary; in this section the following four subgroups are discussed, viz:

1. Mineral acids and alkalies.
2. Phenol and chemically related organic compounds.
3. Inorganic oxidizing agents.
4. Alkaloidal reagents.

MINERAL ACIDS AND ALKALIES

Mineral acids and alkalies, strong acid and basic salts, and organic acids such as oxalic and acetic acid, and so forth, are included in this group. The common factor responsible for injury is the H⁺ or OH⁻ concentration, respectively. Irreversible alteration will occur if the pH is below 2.5 or above 11.5.⁴ A difference between the injury produced by an acid and an alkali is the tendency of the latter to progress by direct extension.⁵ Presumably since alkaline proteinates are soluble, it is possible for the OH ion to pass successively from one molecule to another, denaturing each in turn, without becoming immediately inactivated. On the other hand, the H⁺ seems to be neutralized immediately at point of contact. Other factors responsible for corrosive injury may include coagulation, precipitation, dehydration, or actual solution of protein. Even thermal injury may be superimposed upon the chemical insult, for example, in the case of concentrated H₂SO₄.

Pathologic Changes.—Following ingestion of a corrosive agent, there may be immediate collapse and rapid death. Characteristically, there are lesions of the oral cavity and esophagus.⁶ In the stomach, the pathologic changes are striking. Immediately on receiving the chemical, the organ tends to contract sharply, thereby limiting the initial necrotizing effect to the eminences of the rugae. Stimulation of still intact glands at the depths of the folds leads to outpouring of mucus which covers the surface. The appearance of the necrotic mucosa may serve to identify the responsible corrosive. Sulfuric acid characteristically blackens and chars the tissue. Hydrochloric acid produces white to gray-brown discoloration, while the lesions of nitric acid may have a yellow component because of xanthoprotein. In contrast, the alkalies produce lesions which are usually softer and more edematous. With an increase in the survival time, the lytic effects of the digestive enzymes and the development of secondary bacterial infection make the differential diagnosis progressively more difficult.

In acute corrosive injury when death is rapid, a zone of superficial mucosal necrosis, bordered on its submucosal aspect by hyperemia and edema, may be all that is to be seen. Later, extension of this zone of necrosis may progress to submucosa, depending upon the extent to which its cellular components have undergone irreversible injury. Secondary thrombosis of vessels may add to the damage. Leukocytes gradually accumulate at the base of the lesion. Incident to their disintegration, the released proteolytic enzymes lead to liquefaction and finally to sloughing away of the necrotic material. Repair may be followed by the formation of dense avascular scar tissue. Stenosis of the esophagus is a common sequel to such scar formation. Incomplete regeneration of the epithelium over the cicatrix of a chemical injury may lead to chronic ulceration. In the event of secondary bacterial invasion, the reaction may become suppurative within a few days. The laying down of fibrin on the injured surface may lead to a diphtheritic-like membrane.

Complications.—Early complications of the ingestion of a corrosive agent include rapid circulatory collapse and shock and perforation of the stomach or intestine. It should be borne in mind that massive malacia of the stomach or lower portion of the esophagus may represent a postmortem artefact. Respiratory injury, principally acute laryngeal and pulmonary edema, may occur following aspiration, particularly if the corrosive is volatile. The most common late complication is cicatrizing esophageal stenosis. All other factors being equal, the lesion occurs more commonly with alkaline agents.

Hydrofluoric and Oxalic Acids.—These acids are systemically toxic. Small amounts of hydrofluoric acid taken by ingestion may be rapidly fatal. Spilling of the concentrated acid upon the skin may lead to injury that is extremely slow in healing. Partially this is due to ischemic necrosis from intense local vasoconstriction produced at the site of contact.⁷ Injection of a calcium salt at the site of the local lesion may partially negate the deleterious effect.

A strong corrosive, oxalic acid frequently may be ingested accidentally due to its physical resemblance to magnesium sulfate. The systemic toxicity is due to removal of calcium ions from tissue fluid incident to formation of insoluble calcium oxalate, reflected clinically by mild to severe manifestations of hypocalcemia.⁸ Delayed deaths may be due to kidney injury.

Concentration of oxalate at the portal of excretion may lead to degeneration and necrosis of the tubular epithelium of the kidney.⁹

PHENOL AND OTHER ORGANIC CORROSIVES

Ingestion of phenol or cresol may cause a firm, thick, moderately dry, dull gray to brown eschar. Since these compounds are excellent fixatives, there may be remarkably little microscopic alteration in the chemically killed mucosal cells (Fig. 102). The splashing of phenol upon the unbroken skin has been reported to have caused rapid collapse and death, apparently due to depression of the central nervous system.¹⁰ The postmortem pathologic findings in such instances are insignificant. In delayed deaths the urine may be smoky and aromatic due to oxidized phenol derivatives. The color becomes progressively darker on standing. Routine testing for glucose will give a "false" reaction. An acute hemolytic action has been attributed to di- and trihydroxy phenols which are reducing compounds.¹¹ Atmospheric exposure to hydroquinone, one of the dihydroxy phenols, is said to be responsible for corneal and conjunctival pigmentation, apparently from desposition of polymerized products.¹² This condition could be referred to as "local ochronosis" as contrasted to systemic ochronosis following long continued phenol absorption.¹³

FORMALDEHYDE

Following ingestion of formaldehyde, the esophagus and stomach may become a shrunken gray and somewhat tough and elastic structure, resembling the usual fixed tissue seen in pathologic specimens. If death is delayed, the mucosa may be converted to a friable eschar.¹⁴ Inhalation of the vapor gives rise to irritation in the upper respiratory tract. The injection of a 10 per cent solution of formaldehyde through the abdominal wall and into the cavity of the gravid uterus is sometimes used for the induction of abortion.

INORGANIC OXIDIZING AGENTS

Of the numerous inorganic chemicals having oxidizing properties, the agents most commonly encountered in human poisoning are the permanganates and chlorates. Local injury is dependent primarily upon denaturation of protein by oxidation. An acute systemic effect is intravascular hemolysis.¹⁵ Conversion of freed hemoglobin to methemoglobin is a secondary effect. Lower nephron nephrosis has been described in cases of delayed fatal poisoning.¹⁶ Necrotizing injury of vagina and cervix following insertion of permanganate tablets (0.3 to 0.6 Gm.) as an abortifacient apparently is a not infrequent occurrence.¹⁷ A sequel may be distorting fibrosis of the lower reproductive canal. Although an oxidizing agent, dichromate does not produce significant hemolysis.¹⁸

ALKALOIDAL REAGENTS

These chemicals are mentioned for the sake of inclusiveness. The corrosive effect of members of the group is due to the ability of the

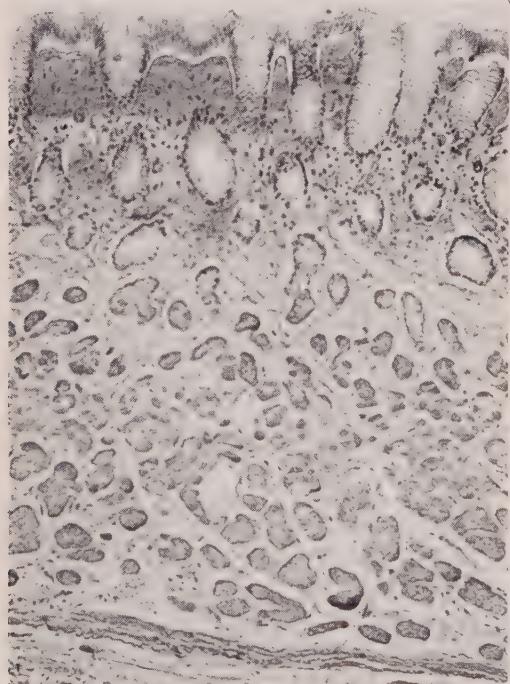


Fig. 102. Stomach in acute phenol poisoning. The superficial portion of the mucosa has been fixed by the chemical and shows excellent histologic detail. The unfixed, deeper portions have undergone postmortem autolysis.

anion to direct chemical precipitation of protein by the anion. The principal alkaloidal reagents are trichloroacetic acid, tungstic acid, picric acid, sulfosalicylic acid, phosphomolybdic acid, and tannic acid. The two compounds most important from the practical standpoint are tannic and picric acids. Hepatic injury may follow absorption of tannic acid applied at the site of cutaneous burns. The pathologic lesion initially is located in the central portion of the liver lobule but by extension may lead to confluent involvement and death. Experimental tannic acid hepatic necrosis has been produced by subcutaneous,¹⁹ intraperitoneal, and intravenous injection,²⁰ and by painting denuded skin surfaces. It would appear that tannic acid is contraindicated in the treatment of burns.

Mild systemic toxicity has been attributed to picric acid (trinitrophenol) following cutaneous absorption.²¹ In dogs, the compound has been shown to be nephropathic.²² Nearly all of a ship's crew were found to develop asymptomatic hematuria following picric acid contamination of the water supply.²³

Gases and Other Atmospheric Contaminants

Chemical injury caused by gaseous substances may occur locally at the sites of initial contact with skin or mucous membrane, or systemically following absorption. The individual compounds comprising the poison-gas group may exist in the atmosphere as true gases, as vapors emanating from liquids or solids, or as finely dispersed liquid droplets. Noxious gases and vapors may be divided into three groups according to their toxic action: (1) irritants; (2) asphyxiants; (3) systemic intoxicants; (4) "war gases."

PULMONARY IRRITANTS

Pulmonary irritants may be encountered in a wide variety of occupations and incident to any conflagration. Having little or no systemic effect, these gaseous substances injure particularly places where a moist surface and delicate epithelium are encountered, thereby favoring the solution and localization of the chemical agent.

The tissue response to any irritating gas is qualitatively similar. Although massive exposure may lead to direct necrosis and ulceration, the concentration of the irritant is rarely of sufficiently high magnitude to accomplish this type of direct injury. Usually, because of the extreme dilution of the irritant, the initial sign of injury is reactive hyperemia and edema, and later diapedesis and leukocytic infiltration.

The clinical and pathologic manifestations of exposure to an irritating gas depend upon which part of the respiratory tract undergoes greatest injury. The factors determining this selectivity of action are not clear but are dependent, in part, upon the ready solubility of the gas in water, and in part on the rapidity of chemical reactivity of the irritant with body tissue. While obviously there is a good deal of overlapping, Henderson and Haggard²⁴ recognize three groups of irritants: (1) Gases principally

affecting the nose, eyes, and pharynx—ammonia is an example of such an irritant. The symptoms are those of an acutely developing coryza, which constitute a warning signal of exposure. Rarely is poisoning fatal. Following excessive exposure there may be necrotizing pharyngitis and tracheobronchitis. There is ulceration and sloughing of the mucosal epithelium, while the underlying tissue becomes edematous, hemorrhagic, and infiltrated by leukocytes and fibrin. Secondary bacterial infection may lead to fatal bronchopneumonia. Rarely, death may be caused by acute laryngeal edema. (2) Gases principally affecting trachea and larger intra-pulmonary air passages. Halogens, halogen acids, sulfur dioxide, and acrolein are examples of such irritants. The first symptoms may be those of mild coryza. Following a latent period of several hours, the subsequent development of air hunger points to involvement of deeper respiratory structures. Death within the first twelve to twenty-four hours is usually associated with hemorrhagic edema in the centrally located pulmonary lobules. The pathogenesis is dependent upon differences in the susceptibility of bronchial and alveolar epithelium to injury. A gas concentration inadequate to cause severe damage to bronchial and bronchiolar mucosa may still be sufficiently high to cause injury to the more delicate endothelium of the alveolar capillaries. Thus, exudation at the site of the centrally located alveolar ducts and communicating alveoli that have the shortest and most direct connections with the bronchi at the hilum may lead to rapidly fatal edema. Focal patches of atelectasis and emphysema and early bronchopneumonia may develop within the first twelve to twenty-four hours. (3) Gases principally affecting the pulmonary parenchyma include the oxides of nitrogen and phosgene. Fatal exposure may occur in the absence of a detectable odor. There is a characteristic latent period before onset of dyspnea unless the exposure has been overwhelmingly severe. In fatal cases, there is severe cyanosis. Frothy blood-tinged fluid pours from the mouth and nares and fills the larger air passages. The heart is acutely dilated; there is severe hyperventilation of all organs, and usually there are disseminated petechiae on serous surfaces. The lungs are heavy, voluminous, and waterlogged. From their red to purple moist sectioned surfaces, copious quantities of pink frothy liquid can be expressed. The alveoli are largely filled by serous fluid rich in protein and contain varying numbers of extravasated red blood cells. Focally, there are areas of emphysema and atelectasis. With the passage of time, secondary bacterial infection may lead to focal or confluent bronchopneumonia.

In nonfatal exposures of this sort, destruction of bronchial mucosa is likely to occur in both large and small air passages. Ulcers in the former usually heal by regeneration, whereas organization and obliterating fibrosis commonly occur in repair of such lesions in the small air passages. Such an obliterative bronchiolitis leads to permanent reduction in vital capacity and may predispose to subsequent episodes of pulmonary infection.²⁵ It might be expected that inhalation of irritant gases and fumes

would predispose to secondary infection of the respiratory tract. This is likely only when exposure has been heavy. Statistically, there seems to be no increased incidence to respiratory infections incident to prolonged exposure to low concentrations of air contaminated by sulfur dioxide, chlorine, oxides of nitrogen and other irritant gases.²⁶

CHEMICAL ASPHYXIANTS

Carbon monoxide and cyanide are conventionally designated as the two principal chemical asphyxiants. A definition based on the modern concepts of asphyxia as advanced by Henderson and Haggard is that asphyxiation represents a "perversion of chemical life processes of the

formed whenever carbonaceous material is burned and atmospheric concentrations up to 30 per cent may occur. Other common sources include illuminating gas and exhaust gas of internal combustion engines. The inhalation of a 1 per cent concentration may be fatal to a resting man in twenty to thirty minutes and to a working man in ten minutes. Due to a higher rate of respiratory exchange, children are likely to die more rapidly than are adults when both are exposed to the same atmospheric concentration. In acute deaths the hemoglobin may be saturated by carbon monoxide to 60 per cent or more. In persons dying a few hours after having been removed from the noxious atmosphere, the per cent saturation may decrease to as low as 20 per cent.

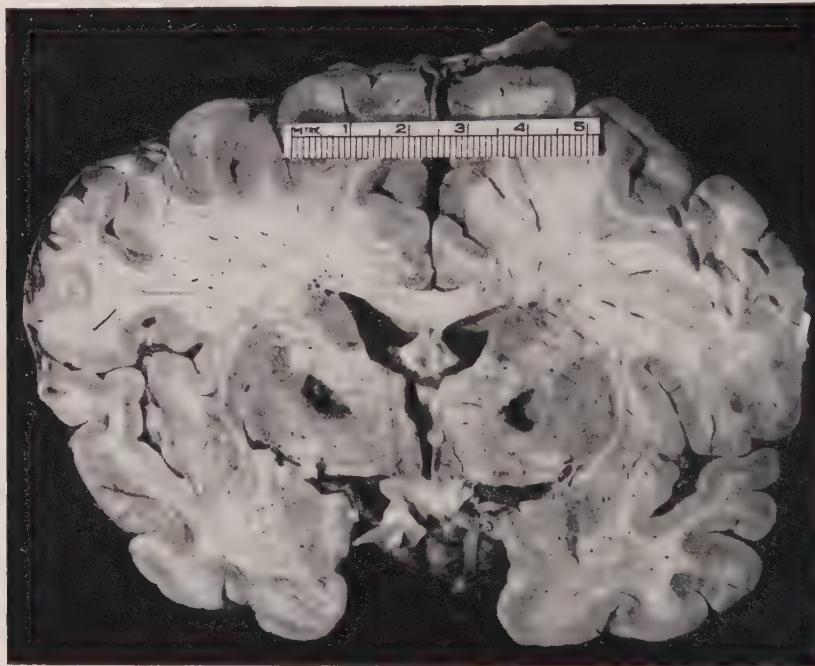


Fig. 103.—Delayed pathologic manifestations of acute anoxia. Nonspecific bilateral symmetrical cystic degeneration of the globus pallidus in patient surviving ten months following severe carbon monoxide asphyxiation.

tissues under deficiency of oxygen." Since many types of fatal injury, whether chemical or physical, may cause death by interfering with the uptake, transport, or utilization of oxygen, it is clear that the designation of carbon monoxide and cyanide as asphyxiants to the exclusion of many other asphyxiants might appear to be unjustifiably arbitrary. The selection of these two poisons for discussion under the caption of chemical asphyxiants is in recognition of the peculiar directness with which they cause asphyxia.

Carbon Monoxide.—Carbon monoxide, with an affinity for hemoglobin several hundred times greater than that of oxygen, is responsible for a large proportion of all suicidal and accidental deaths by poisoning. Carbon monoxide is

PATHOLOGIC CHANGES.—Characteristically, the viscera, blood, and skeletal muscles are cherry pink due to carbon monoxide hemoglobin. A pink to red color of the skin is not pathognomonic of carbon monoxide poisoning. Anyone who has peripheral vasodilatation at death and whose body lies in the cold may develop this color. If the peripheral vessels remain contracted, the skin may be pale even in the presence of a high blood concentration of carbon monoxide. Petechial hemorrhages are not a prominent feature in rapidly fatal poisoning.

The death of most people who perish at the place of and because of a conflagration is due to acute carbon monoxide poisoning. In such instances, the inhalation of various irritating combustion products before death is indicated by the

presence of extensive carbon deposits and a large amount of mucus throughout the air passages.

DELAYED PATHOLOGIC MANIFESTATIONS OF ACUTE ANOXIA.—It frequently is the case that people die some time after the acute episode of carbon monoxide gassing. When the degree of acute anoxia is insufficient to cause immediate death, destruction occurs at sites particularly susceptible to anoxic injury, notably in the central nervous system. The cerebral cortex and the gray matter of the corpus striatum is specifically affected. Microscopically in anoxic injury the cerebral cortex may be destroyed focally or diffusely. Reactive gliosis at the site of such lesions may be prominent. Demyelination may be seen primarily or secondarily where actual destruction has occurred previously. Peripherally about sites of destruction there may be found marked perivascular reaction by chronic inflammatory cells.

necessarily the site of gross destructive lesions. We have observed bilateral symmetrical lesions in hypothalamus, thalamus, and, in a recent case, in the insula and external capsule in simply produced anoxia. Some attempt has been made to differentiate locale of pathologic change on the basis of the action of the noxious agent,²⁷ particularly on the specific phase of carbohydrate metabolism which may be blocked and the richness or paucity of an area in the enzyme inhibited. It should be emphasized that all of the various types of anoxic lesions reported upon have been duplicated by Morrison.²⁸ This investigator working with high altitude anoxia caused variable results by varying the number of exposures, their duration, number, severity, and the rate in which they were induced.

Cyanides.—Cyanides are toxic because they inhibit the action of the intracellular oxidative

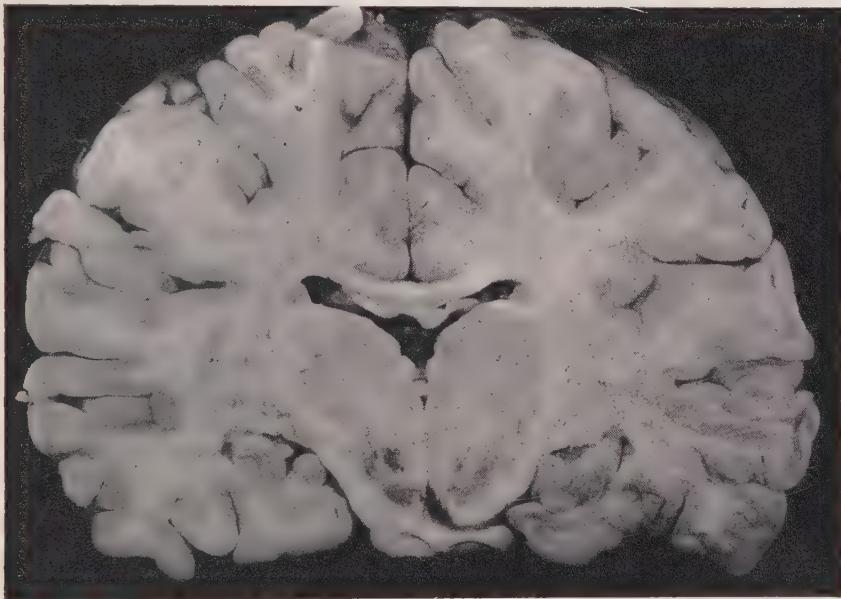


Fig. 104.—Delayed manifestations of acute anoxia. Bilateral symmetrical necrosis in hypothalamus and subthalamus in patient dying six days following respiratory arrest during anesthesia.

Another change is leptomeningeal edema, fibroblastic infiltration, and chronic inflammatory cell infiltration. Seen in various types of anoxic disease these abnormalities are highly non-specific; they may be seen in heavy metal poisoning and indeed in disease caused by infectious and other agents, notably the viruses. Basically, the nervous system is limited in the way in which it reacts to an injurious insult regardless of its nature. That damage has taken place can be determined; what was the cause of the damage cannot be so easily appraised.

What seems to be characteristic in anoxic injury, regardless of its cause, is the bilateral symmetry of the lesion from the standpoint of the gross pathologic changes. Although occurring usually in the lenticular nucleus, especially the globus pallidus (Fig. 103), these areas are not

enzymes. The common compounds are the gaseous hydrocyanic acid and cyanogen and the solid potassium and sodium cyanides.

PATHOLOGIC CHANGES.—Although carbon dioxide is not increased in cyanide poisoning, disseminated petechiae are usually a prominent feature. This manifestation of severe vascular injury may be contributed to by the violent convulsive seizures that frequently occur. In addition to the characteristic cyanide odor, a pink-red color of blood, tissues, and skin is sometimes observed. Cyanide does not combine with hemoglobin but does with methemoglobin. Methemoglobin, which is a postmortem conversion product of hemoglobin, reacts with cyanide to form the colored cyanmethemoglobin (Henderson and Haggard). Ingestion of sodium or potassium

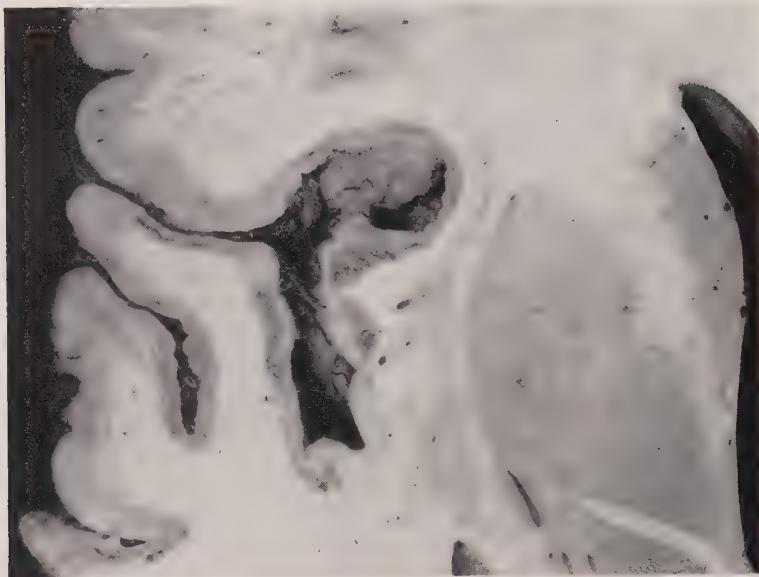


Fig. 105.—Delayed manifestations of acute anoxia. Necrotic softening and shrinkage in insular and temporal cortex in a patient dying one year after cardiorespiratory arrest incident to anesthesia. The lesion was bilaterally symmetrical. Shown is part of one side of a coronal section. Note the normal appearance of the lenticular nucleus. The vessels are hyperemic and there is increased vascularization in relation to the necrotic areas.

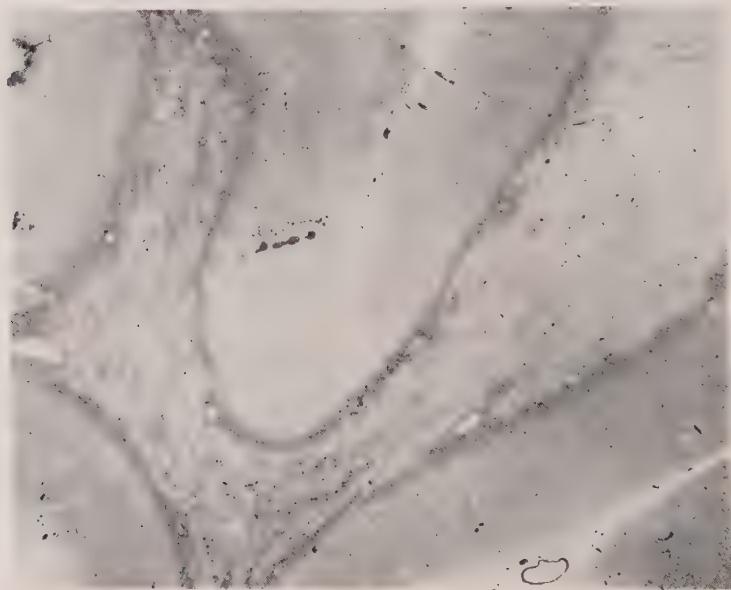


Fig. 106.—Delayed pathologic manifestations of acute anoxia. Focal and confluent destructive lesions in subcortical white matter of frontal lobe in patient dying six weeks after a single exposure to carbon monoxide. (Weil myelin stain $\times 20$). See also Figs. 107 and 108.

salts of cyanide leads to superficial hemorrhagic necrosis of the stomach.

CHRONIC CYANIDE POISONING.—Vague nervous system and gastrointestinal symptoms have been attributed to repeated occupational exposure to cyanide. Another suggested effect is diffuse or adenomatous goiter. The detoxified product of cyanide,²⁹ thiocyanate, is said to result in decreased uptake of iodine.

SYSTEMIC INTOXICANTS

Arsine.—Arsine, the hydride of arsenic, is an acute hemolytic poison. The gas is produced whenever an acid reacts with a crude metal (most crude metals are arsenic-containing).



Fig. 107.

Fig. 107.—Hematoxylin-eosin preparation from same area shown in Fig. 106. The destructive lesion is characterized by astrocytic proliferation and macrophagic response. ($\times 225$)

Fig. 108.—Subependymal gliosis of third ventricle in same case shown in Figs. 106 and 107. (Nissl $\times 400$.)

There is usually a latent period of several hours before manifestations of the acute hemolytic reaction appear.³⁰ Death may occur acutely at this stage or may be delayed for several days incident to the development of progressively increasing renal insufficiency. The renal lesion is the lower nephron nephrosis described by Lucké.³¹

Hydrogen Sulfide.—Hydrogen sulfide gas may be evolved whenever organic material decomposes and is the main component of sewer gas.³² Large doses lead to profound depression of the central nervous system. Locally, hydrogen

sulfide is necrotizing to the lining of the upper respiratory passages.³³ In fatal cases, the tissues and liver may be gray-green. This color is said to be due to sulfmethemoglobin, a compound formed by the postmortem combination of methemoglobin and hydrogen sulfide.

WAR GASES

These compounds may be true gases, volatile liquids, or solids which disperse upon explosion. The substances generally available during World War II included those which largely acted as local irritants and others which combined systemic toxic effect (vesicants). Lewisite and the nitrogen and sulfur mustard gases are

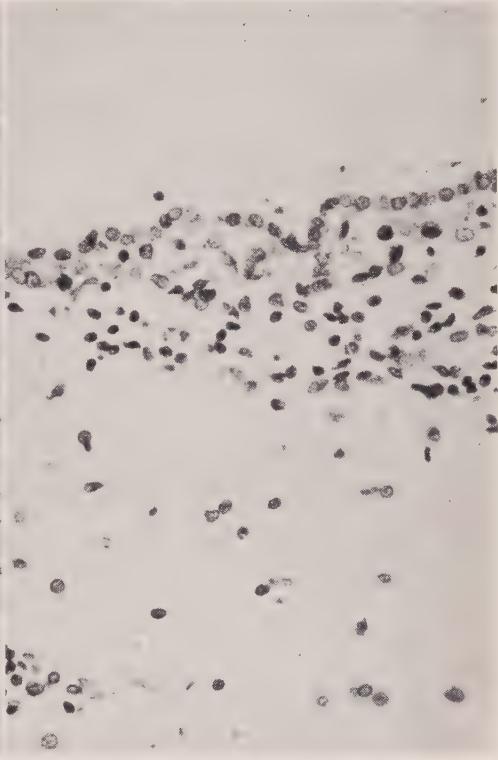


Fig. 108.

vesicant compounds producing rapid necrosis on contact with skin, eyes, and respiratory linings and may be absorbed following skin application, ingestion, injection, and to a lesser extent from inhalation. The manifestations of systemic lewisite poisoning are similar to those of inorganic poisoning.³ Acute intravascular hemolysis resembling that produced by arsine has been produced experimentally.² The systemic effect of the mustard gases is degeneration of blood-forming organs. Employed in the treatment of leukemia, Hodgkin's disease, lymphosarcoma, and similar diseases, toxic

manifestations may be neutropenia, lymphopenia, thrombocytopenia, and mild to moderate anemia.^{34, 35} Recent evidence indicates these agents may be cancerigenic.³⁶

Much more toxic than the formerly known agents of chemical warfare are organic phosphates referred to as "nerve gases."^{37, 38} Some of these compounds are used therapeutically in myasthenia gravis and in the management of urinary retention and abdominal distention, viz., diisopropyl fluorophosphate (DFP),³⁹ tetraethylpyrophosphate (TEPP). Organic phosphates such as O, O-diethyl O-paranitrophenyl thiophosphate tetraethyl phosphate (parathion) and hexaethyltetraphosphate (HETP) are also highly potent insecticides against mites and soft bodied insect pests. The effects of the organic phosphates can be explained on the basis of their

Metallic Poisons

Metals, as a class, have diffuse systemic toxicity and frequently are referred to as protoplasmic poisons. Because of their slow elimination, repeated small doses tend to have a cumulative action. Although all parts of the body are affected, injury is usually most severe at sites of entry and elimination, where the highest concentrations occur. Other sites of special vulnerability include the central and peripheral nervous systems. Many metals probably act as enzyme inhibitors. Protection of cells from the injurious effects of arsenic, mercury, gold, and cadmium to 2, 3-dimercaptopropanol (BAL) suggests that the primary biochemical lesion may be blocking of metabolic processes by combination of metal with sulfhydryl groups of enzyme proteins.⁴² The



Fig. 109.—Acellular areas and hyperchromic neuronal cells in cornu ammonis in insulin hypoglycemia, another delayed pathologic manifestation of acute anoxia. (Nissl $\times 160$) (From J. Neuropath. & Exper. Neurol. 11: 319, 1952.)

ability to inhibit cholinesterase.⁴⁰ The toxic manifestations may include central nervous system depression and acute bronchoconstriction and are said to resemble combined muscarine-nicotine poisoning. Occupational deaths following accidental handling of parathion and other organic phosphates have been reported. In one case the postmortem cholinesterase activity was found to be reduced.⁴¹ There were no specific pathologic findings. Information pertaining to organic phosphate compounds adaptable for chemical attack is largely classified. It may be presumed such compounds are available and that their toxicity is even greater than those known compounds mentioned here.

similarity between the manifestations of arsenic poisoning and acute thiamine deficiency is in accord with this hypothesis.⁴³

INORGANIC ARSENIC

Inorganic arsenic is a generalized poison with a special predilection for the vascular endothelium. The usual route of entry is by ingestion. Commonly available preparations include arsenic trioxide, arsenites of lead, sodium, and potassium, arsenical insecticides, and arsenic-containing wall paper and paints.

The clinical characteristics of acute poisoning are intense abdominal discomfort, vomiting, and diarrhea, followed by rapid circulatory

collapse. Death may occur within a few days and sometimes in less than one hour.

Pathologic Anatomy.—Postmortem examination characteristically discloses severe visceral hyperemia, disseminated petechiae which are likely to be particularly prominent beneath the endocardium, and effusions of edema fluid into the serous cavities. The longer the period of survival after ingestion of the poison, the more prominent will be the evidence of injury of the gastrointestinal tract. The gastric mucosa may become extensively ulcerated in the prepyloric region. Nervous system lesions are nonspecific.⁴⁴ Injury may be manifested by diffuse degenerative changes with evidence of leakage of plasma, red blood cells, or both, through the damaged capillaries. The cerebral vessels may become occluded by cellular or hyaline thrombi. Perivascular zones of hemorrhagic necrosis may be encountered in the brain.⁴⁵ Other degenerative changes occasionally seen in acute poisoning include focal hepatic necrosis and degeneration of the renal tubular epithelium.

CHRONIC ARSENIC POISONING

The principal signs and symptoms of chronic poisoning may be referable to the skin, the gastrointestinal tract, the nervous system, or any combination of these.

Pathologic Anatomy.—Chronic poisoning may lead to focal and confluent dark brown to black patches of cutaneous pigmentation, particularly at sites which are normally pigmented.⁴⁶ The pigment is thought to be a melanin derivative. Hyperkeratosis may be the outstanding cutaneous manifestation of chronic poisoning and characteristically involves the palmar surfaces of the hands and the plantar surfaces of the feet. Such hyperkeratotic lesions may undergo conversion to squamous carcinoma.

The pathologic manifestations of chronic arsenic poisoning in the gastrointestinal tract are qualitatively similar to, but quantitatively milder than, those of acute poisoning. Nutritional deficiency incident to the gastrointestinal upset may complicate the pathologic picture. Probably the most common manifestation of chronic arsenic poisoning is a degenerative change in the peripheral and particularly in the sensory nerves. These changes are evidenced by myelin degeneration with accompanying tortuosity and swelling of the axis cylinders. According to the investigations of O'Leary, Snell, and Bannick,⁴⁷ the administration of arsenic over long periods of time may be responsible for progressive degeneration of the liver, leading to a portal type of cirrhosis. For a discussion of potentially dangerous sources of arsenic in everyday life, see Cannon.⁴⁸

ORGANIC ARSENIC

Organic arsenic poisoning occurs principally during antisyphilitic treatment. The nitritoid or Herxheimer phenomena, which occasionally take place during or immediately following the injection of an arsenical agent, are manifested

by an acute shocklike reaction with or without angioneurotic edema.⁴⁹ The pathologic findings are not characteristic.

It has been estimated that one in every 25,000 patients receiving antisyphilitic treatment dies of a delayed reaction to arsenic.⁵⁰ The cause of such individual hypersusceptibility is not clear, but therapeutic benefit from the administration of BAL suggests that the active toxic agent may be inorganic arsenic.⁵¹ The nervous system, liver, skin, or hemopoietic systems may be involved. The pathologic lesions of delayed poisoning due to the administration of organic arsenical agents are: (1) acute encephalopathy; (2) diffuse hepatic necrosis; (3) dermatitis of varying acute and chronic types; (4) depression of hemopoiesis involving red cells, granulocytes, or platelets, or any combination of these.⁵² The lesions in the brain and liver are qualitatively similar to those produced by inorganic arsenic.

SELENIUM AND TELLURIUM

Selenium and tellurium are closely related chemically and possess toxic actions similar to those of arsenic. The hydrides are acute hemolytic poisons. Selenium and tellurium are used in alloys and in colored glass. The common compounds are the oxides and sodium salts.

Acute poisoning in man has been reported following the accidental ingestion of sodium tellurite.⁵³ There may be no significant findings other than a garlic-like odor of tissues. Chronic experimental poisoning by ingestion of tellurium oxide leads to focal and confluent hepatic necrosis and to degeneration of the renal tubular epithelium.⁵⁴

In certain sections of the country, referred to as seleniferous belts, the soil is rich in selenium. Cattle feeding upon grass and grain grown in such areas may develop chronic selenium poisoning, referred to as "blind staggers" and "alkali disease."⁵⁵ In its fully developed form, this disease may be manifested by ulcerative gastroenteritis, focal or diffuse hepatic necrosis, and nephrosis.

INORGANIC LEAD

The principal toxic action of inorganic lead is that of a generalized cumulative protoplasmic poison. Children seem to be more susceptible than adults.⁵⁶ The principal portals of entry are the gastrointestinal tract and the lungs. Common sources of domestic poisoning include paint, water carried in lead pipes, and plant sprays. Industrial poisoning principally by inhalation may occur during refining and smelting processes, and during the manufacture of numerous lead-containing compounds.^{57, 58, 59, 60}

Acute poisoning due to the ingestion of a soluble lead salt leads to the signs and symptoms of gastroenteritis. The acuteness and severity of the clinical manifestations of lead intoxication by inhalation or ingestion depend upon: (1) amount of exposure; (2) rate of absorption; (3) the extent to which circulating lead is deposited in bone; (4) the presence or absence of factors tending to release stored lead into the general circulation. Signs and symptoms of poisoning most frequently point to involvement of the gastrointestinal, nervous, and hemopoietic

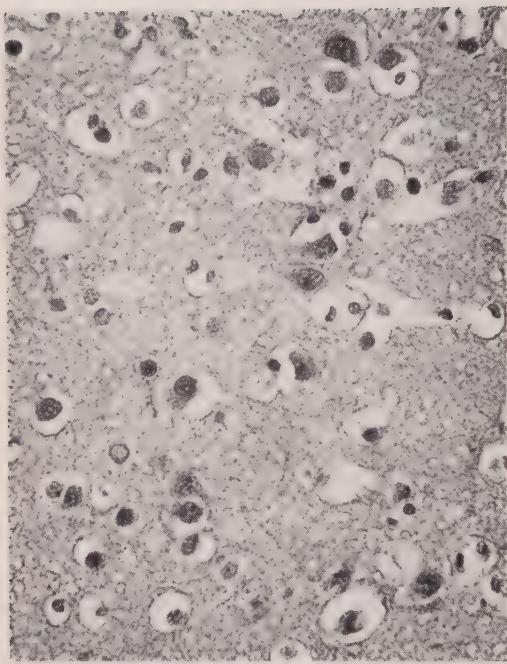


Fig. 110.—Acute lead encephalopathy. Cerebral edema with vacuolation of interstitial tissue, prominent pericellular clear zones, and oligodendroglial swelling.

systems.^{61, 62} An interesting finding in lead poisoning is acid-fast nuclear inclusion bodies in the liver and the kidney.^{63, 64} Roentgenographic evidence of skeletal deposits cannot be expected to appear in less than three to six months, even with daily absorption. For a discussion of the significance of urinary and blood lead values, see Castrop⁶⁵ and Patty.⁶⁶

Pathologic Findings.

GASTROINTESTINAL SYSTEM.—The spasmotic contractions of the intestinal muscle in lead colic are due to the concentration of that element in the blood rather than to enteritis, and as a rule there is little or no gross or microscopic evidence of mucosal injury. The "lead line" of the gums is a perivasculär deposit of lead sulfide in the submucosal papillae.

NERVOUS SYSTEM.—*Acute Encephalopathy:* This condition may be caused by a single large dose or from the cumulative effect of repeated small exposures. In fatal cases the outstanding manifestations are coma with convulsive seizures that may be uncontrollable. The pathologic findings in the brain may vary from minimal or no change to that of a diffuse, nonspecific encephalopathy with acute neuronal degeneration, swelling of the vascular endothelium, perivascular and diffuse edema, and fibroblastic proliferation of the leptomeninges.⁶⁷ Calcification in the walls of blood vessels occurs rather characteristically, although it is not pathognomonic of poisoning by lead. Residual nervous system injury may be a serious permanent complication in persons sur-

viving the acute phase of the intoxication,^{68, 69} particularly in children.

Peripheral Neuropathy: The lesions are said to occur in motor nerves and particularly those to muscles showing the greatest fatigue.⁷⁰ The principal pathologic change is myelin degeneration, which may slowly progress to irreversible alterations of the axis cylinders.

HEMOPOIETIC SYSTEM.—One of the most common findings in lead intoxication is basophilic stippling of circulating erythrocytes and a mild anemia.^{71, 72} This type of stippling is thought to be due to the formation of lead phosphate on the surfaces of the red cells. Reticulocytes of the peripheral blood and bone marrow are most commonly affected. The bone marrow may show mild normoblastic hyperplasia.

ORGANIC LEAD (TETRAETHYL LEAD)

The outstanding toxic action of tetraethyl lead is its effect in the central nervous system. Fatal poisoning has occurred following inhalation of the vapors.⁷³ The symptomatology includes acute delirium, convulsive seizures, and progressively increasing coma.⁷⁴ Cerebral vascular injury may be manifested by perivascular and diffuse edema and partially or completely occluding cellular or hyaline thrombi in the smaller vessels. Circulating tetraethyl lead may injure alveolar capillaries, leading to acute pulmonary edema.

MERCURY

The protein-precipitating action of the mercuric ion makes it injurious to all protoplasm. Among the soluble salts which readily dissociate to form the mercuric ion, bichloride of mercury is the compound most commonly responsible for fatal poisoning. The usual portal of entry is the gastrointestinal tract. Intrauterine or intravenous administration of mercurial salts may cause acute intoxication. For a review article on the toxicology of mercury, see Ray and Burch, "Mercurial Diuretics."⁷⁵

Acute Mercury Poisoning.

CLINICAL CHARACTERISTICS.—Following ingestion there is abdominal pain, nausea, and vomiting. Circulatory collapse may lead to death within a few hours. If the initial period of shock is survived, localization of injury in the kidneys may subsequently result in oliguria, anuria, and terminal uremia.

PATHOLOGICAL FINDINGS.—*Gastrointestinal Tract:* The mucosa of the stomach is characteristically destroyed by coagulation necrosis. Since the agent is excreted as well as absorbed by the gastrointestinal tract, the gastric damage by ingested mercury is likely to be followed by injury to the mucosa of the colon. The longer the period of survival after ingestion, the more severe the excretory lesions in the colon become. The ulcers in the large bowel may lead eventually to a most profound necrotizing and hemorrhagic process complicated by secondary bacterial infection.

Kidneys: Mercury and certain other nephrotoxic agents are especially injurious to the epithelium of the proximal convoluted tubules because

it is in this segment of the nephron that the maximum concentration of the poison is reached.⁷⁶ Oliguria and anuria may be explained by the backward diffusion of the aqueous component of the glomerular filtrate through the injured tubular epithelium and by obstruction of the tubular lumina by precipitated protein, desquamated necrotic epithelium, and casts.

The nature of the pathologic changes in the kidneys of bichloride poisoning depends upon the duration of the survival period. The earliest recognizable change is coagulation of the epithelium of the proximal convolutions, followed by nuclear fragmentation and cellular disintegration. The necrotic cells desquamate, and later hyaline, granular, and leukocytic casts are formed. Calcium may be deposited in degenerating epithelium or in the detached necrotic masses of cells lying

partially occluded by exuberant masses of multinucleated cells.⁷⁷ Mitotic figures may be numerous. By the end of the second or third week, the histologic picture is usually dominated by regenerative activity. Complete reversal to normal function and morphologic appearance may be expected if the poisoning is survived beyond the first four to five weeks.

MERCURIALISM.—Exposure to metallic mercury^{78, 79, 80} may be followed by toxic symptoms, acute or chronic, which basically are different from those caused by acute administration of mercurial salts. The principal manifestations of acute mercurialism are stomatitis and digestive upset. Chronic mercurialism involves primarily the central nervous system and is characterized by fine intention tremor, exaggerated tendon reflexes, emotional instability, erythema, and hyper-

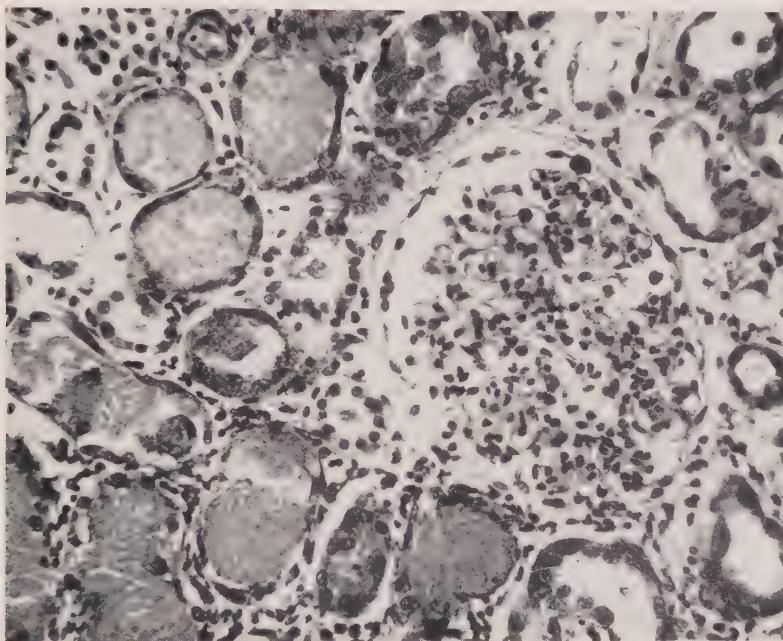


Fig. 111.—Necrosis and desquamation of epithelium of convoluted tubules and cast formation in bichloride of mercury poisoning. The low nongranular darkly staining cells indicate early regeneration. Death occurred at the end of the second week from uremia.

in the lumen. Although the degenerative and necrotizing effects may come to involve the epithelium of both the proximal and distal convolutions and the loops of Henle, the glomeruli rarely show evidence of injury beyond the presence of protein in the capsular space. Grossly, the kidneys appear large and pale and the cut surfaces reveal swollen and red-gray cortices with obscuration of the corticomedullary boundary. Regeneration of tubular epithelium occurs early, and evidence of both regeneration and degeneration may be seen in contiguous areas (Fig. 111). The regenerated epithelium forms a flattened layer of nongranular, darkly staining cells between the necrotic cells and their basement membrane. Regeneration may proceed to the point where tubules become par-

hydrosis. Evidences of renal irritation are minor or absent. The pathologic lesions in chronic mercurialism are incompletely known but from clinical appraisal it would appear that they are located in cerebral cortex and extrapyramidal areas. Intoxication of a somewhat similar nature has been described following exposure to diethyl⁸¹ and methyl mercury compounds,⁸² both fungicidal agents.

BISMUTH

The toxic effects of bismuth are similar although less severe than those of mercury. The more commonly available compounds are of such low solubility that poisoning by ingestion is exceedingly rare. Mild poisoning is occasionally encountered in persons receiving intra-

muscular injections of bismuth during treatment of syphilis. Severe and even fatal poisoning has been observed following the application of bismuth paste to open wounds.⁸³ Like mercury, bismuth is excreted both by the kidneys and by the mucosa of the colon and may result in severe degeneration and necrosis of the tubular epithelium and in ulcerative colitis. Unlike mercury, bismuth poisoning is associated with the presence of acid-fast inclusion bodies in renal epithelium.⁸⁴

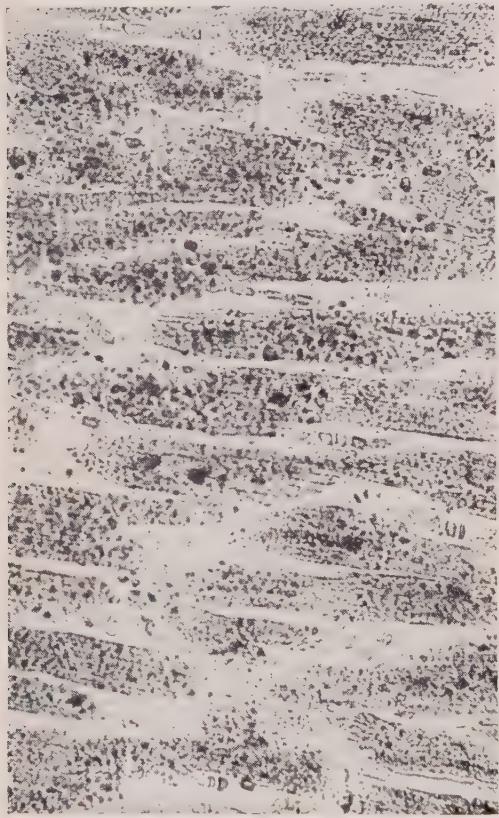


Fig. 112.—Heart in acute phosphorus poisoning. Death occurred thirty-six hours following ingestion of rat poison. Extensive sudanophilic accumulations are represented by fine and coarse black stippling. No counterstain was used.

The methemoglobinemia which sometimes follows the ingestion of bismuth nitrate is due to the reduction by the intestinal bacteria of the nitrate to nitrite, with absorption of the latter, the toxic effects being caused by the nitrite rather than by bismuth.^{85, 86, 87}

GOLD

Gold is a protoplasmic poison having an action said to be somewhat similar to arsenic.⁸⁸ Human intoxication as a result of therapy in rheumatoid arthritis may lead to toxic reactions including blood dyscrasias,^{89, 90} dermatitis,⁹¹ hepatic necrosis,⁹² nephrosis, and central and

peripheral neuropathy.⁹³ Apparently with the exception of renal injury which rarely assumes grave importance, the reactions may occur unpredictably and without regard to the plasma gold concentration.⁹⁴

THALLIUM

Thallium is a highly toxic cumulative systemic poison. The chief present-day source of thallium is rat poison,^{95, 96} the ingestion of which may be followed by profound circulatory collapse and central nervous system depression. In subacute poisoning, digestive upset and peripheral neuropathy may occur. A delayed manifestation is epilation coming on in the second and third week. The pathologic lesions are not characteristic.⁹⁷ We were unable to find definitive lesions in several children dying seven to fourteen days after accidental eating of thallium rat poison.

MANGANESE AND CADMIUM

Inhalation of many chemicals in particulate form may lead to a type of pulmonary reaction conveniently referred to as "chemical pneumonitis." By the term is meant activation of alveolar cells and the outpouring of these into the alveolar lumen as macrophages. Secondarily, there may be intra-alveolar edema and exudation of inflammatory cells. "Chemical pneumonitis" is not necessarily the result of exposure to simple chemicals; it may also be caused by organic dust such as that found in cotton, wool, and sugar cane, or by aspiration of oil, milk, etc. The sequelae may be uncomplicated resolution although sometimes there may be secondary fibroblastic proliferation sufficient to produce clinical manifestations of pulmonary insufficiency. The only two inorganic substances known to be capable of producing chronic permanent effects are silica and beryllium (viz., pneumoconiosis).

The immediate effects of manganese oxide and cadmium oxide on lung parenchyma are similar. The ultimate effects differ since cadmium is a systemic poison. The spectacular lesion following prolonged exposure to manganese dioxide is said to be nonspecific hepatic necrosis and lenticular degeneration in the brain resembling Wilson's hepatolenticular degeneration.⁹⁸ Cadmium poisoning by ingestion is rare although it has been encountered where there has been suicidal ingestion of the soluble salt.

PHOSPHORUS

Phosphorus is an extremely active protoplasmic poison which depresses cellular oxidation and leads to widespread fatty degeneration. The common sources include certain rat poisons, phosphorescent paints, and the fumes of phosphorus oxide.

Acute Phosphorus Poisoning.—

CLINICAL CHARACTERISTICS.—Large doses may lead to death by depression of the central nervous system, preceded by coma, convulsions, and finally by medullary paralysis.^{99, 100} In delayed acute poisoning the principal clinical disturbances are referable to the hepatic damage.

PATHOLOGIC MANIFESTATIONS.—Even in rapidly fatal cases of poisoning, microscopic examination may reveal extensive fatty degeneration

in all viscera, including the nervous system.¹⁰¹ The changes also are particularly striking in the liver, heart (Fig. 112), and kidneys. In the liver, the initial degenerative changes occur in the peripheral portion of the lobules. The process may lead to extensive hepatic necrosis.

In children who have recovered from phosphorus poisoning, metaphyseal bands of increased density have been observed in long bones.¹⁰² Similar metaphyseal alterations may occur after many acute illnesses, and after intoxication by arsenic, lead, bismuth, strontium, and other metals. Adams and Sarnat¹⁰³ regard such skeletal lesions to be nonspecific and to be related to an interference with enchondral ossification during the acute phase of the disease.

Chronic Phosphorus Poisoning.—Chronic phosphorus poisoning usually results from inhalation rather than from ingestion. The characteristic pathologic lesion is a progressive necrotizing and suppurative osteomyelitis of the maxilla or the mandible, with the formation of multiple draining sinuses and extensive disfigurement.¹⁰⁴ Phosphorus also has been incriminated as a possible etiological factor in the production of cirrhosis of the liver.^{105, 106}

URANIUM

Evidence to date indicates that uranium has its principal toxic action on the kidney tubules.¹⁰⁷ Apparently it is unlikely that the substance can accumulate in tissues to the extent of producing general x-irradiation injury. The pathological lesion in the kidney resembles that produced by mercury, chromium, and other metallic nephropathic agents. Pulmonary injury following inhalation is attributable to the acid-radical component, fluoride, for example.

CHROMIUM

Chromium compounds are local irritants and following absorption may act as systemic poisons. The more commonly available compounds are the oxides and chromates. The pathologic lesions following ingestion include necrotizing gastroenteritis and nonspecific degeneration and necrosis of the proximal convoluted tubules of the kidneys.¹⁰⁸ Nonfatal, acute encephalopathy has been described.¹⁰⁹ In experimental dichromate poisoning in rabbits, the principal lesion was renal injury. There was no pathologic evidence of nervous system involvement. About twenty days were required for disappearance of chromium from soft tissues and blood after a single large dose. Chromium was present in bone for periods up to three months.¹¹⁰

In industry, the inhalation of dust and fumes of chromium compounds may give rise to ulceration of the nasopharynx and finally to perforation of the nasal septum. Burrowing and slowly healing cutaneous ulcers (chrome holes) may follow contact at the site of pre-existing small cracks or abrasions in the skin.¹¹¹ That prolonged inhalation of chromium compounds may lead to increased incidence of pulmonary cancer has been reasonably well established.¹¹²

LITHIUM

Lithium, in the form of the soluble chloride salt, has come into prominence recently as a dietary substitute for sodium chloride. In eleven patients symptoms attributable to lithium toxicity occurred with muscular weakness, reflex hyperirritability, tremor, blurring of vision and lethargy.^{113, 114} There were two deaths but without autopsy. The mechanism of action may be biological competition between lithium and sodium, both being closely related chemically. Experimental evidence indicates sodium deficiency enhances the toxicity of lithium.¹¹⁵

BORATES

Borates act as depressants of the central nervous system and are necrotizing to the mucosa of the gastrointestinal tract and to the renal tubular epithelium. The accidental intravenous or subcutaneous injection of boric acid instead of saline or the accidental use of boric acid instead of water in the preparation of infant's feeding formulas is a common cause of fatal poisoning by this agent.^{116, 117} Absorption and systemic poisoning also may occur following the dusting of ulcerative skin lesions or the application of boric acid ointment on cutaneous burns.^{118, 119} It has been suggested that boric acid be recognized as a poison and removed from the *Pharmacopoeia*.

The early signs and symptoms of poisoning by ingested borate include nausea, vomiting, and diarrhea. Later, the subject becomes lethargic and eventually comatose. Convulsive seizures are common. The pathologic changes in the brain include acute neuronal degeneration, endothelial hyperplasia of the blood vessels, and either perivascular or diffuse edema. Necrotizing enterocolitis and nephrosis of varying degrees of severity are associated. People who recover may develop exfoliative dermatitis. Intracytoplasmic inclusion bodies in acinar cells of pancreas have been described in human and in experimental borate poisoning.¹²⁰

FLUORIDES

Fluoride leads to hypocalcemia by inactivation of calcium. It also acts as an enzyme inhibitor,

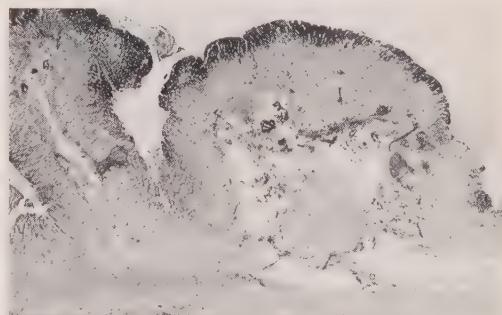


Fig. 113.—Stomach in acute sodium fluoride poisoning. The organ has contracted sharply and the necrotizing effects are limited to the eminences of the rugae.

blocking glycolysis possibly by inactivating magnesium. Fluoride poisoning may be acute or chronic.

Acute Fluoride Poisoning.—Acute poisoning occurs by ingestion. The most common preparation is sodium fluoride, used as an insecticide and roach killer. The best study of fatal acute poisoning was provided by the occurrence of mass poisoning resulting from kitchen help accidentally substituting sodium fluoride for powdered milk in a scrambled egg mixture.¹²¹ The eating of this preparation resulted in 263 persons being made acutely ill, of whom 47 died, many within as little as two to four hours. The signs and symptoms were referable to local gastrointestinal irritation and to systemic manifestations of acute hypocalcemia with principally muscular twitchings and generalized tetany, leading to profound collapse and terminal respiratory failure. The morphologic abnormalities were mild to severe necrotizing gastritis (Fig. 113). The postmortem blood calcium in fatal cases may be as low as 2.6 mg. per cent¹²² (also in acute oxalate poisoning). The rational method of treatment is calcium administration.¹²³

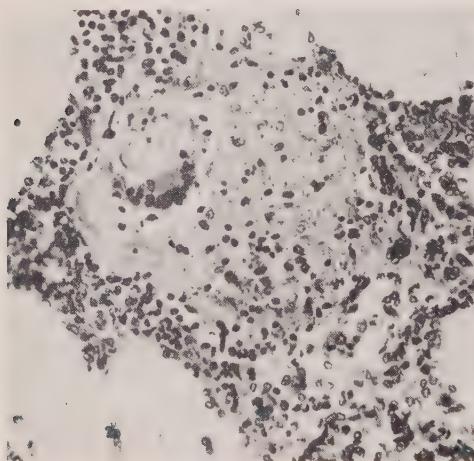


Fig. 114.

Fig. 114.—Beryllium pneumoconiosis. The basic lesion shown here is an intra-alveolar granuloma. Note the giant cell with the peculiar structure contained therein, referred to usually as "conchoidal body." (H & E $\times 325$.)

Fig. 115.—Beryllium pneumoconiosis. A more advanced stage of the disease with fusion of individual lesions and peripheral fibrosis. There is central focal necrosis.

Chronic Fluoride Poisoning.—The principal manifestation of chronic fluoride poisoning is osteosclerosis (Roholm's cryolite fluorosis).¹²⁴ There now is a wide variety of occupations in which toxic exposure may occur, in addition to smelting or other industries where fluoride is used as a flux.¹²⁵ Mottling of the teeth (dental fluorosis) is the result primarily of ingestion of drinking water high in fluoride content. The minimal threshold for dental fluorosis is uncertain; it may be as low as 0.9 ppm.¹²⁶ Evaluation of attempts to prevent dental caries by adding small quantities of sodium fluoride to drinking water is still incomplete.

BERYLLIUM

Within the past several years there have been numerous articles written attesting to the primary toxicity of this metal, in addition to hazards potentially present in the mining and smelting of beryllium, various metallurgic processes, phases of atomic energy development,¹²⁷ and the fluorescent lamp industry (beryllium phosphors). It has been suggested that the essential mechanism in beryllium intoxication is the development of tissue sensitivity.¹²⁸

Acute exposure may be followed by contact dermatitis and acute inflammatory lesions of the conjunctiva, cornea, or oropharynx. A chronic lesion is the subcutaneous granuloma following deposition of beryllium beneath the skin, reported most frequently following wounds produced by broken fluorescent bulbs.^{129, 130, 131} These intradermal lesions are extremely slow in healing and follow the pathologic pattern of the chronic pulmonary granuloma to be described.

Pulmonary Manifestations.—One type is an acute or subacute reaction that may develop after a few months of exposure or less to dusts of beryllium oxide and various salts. The

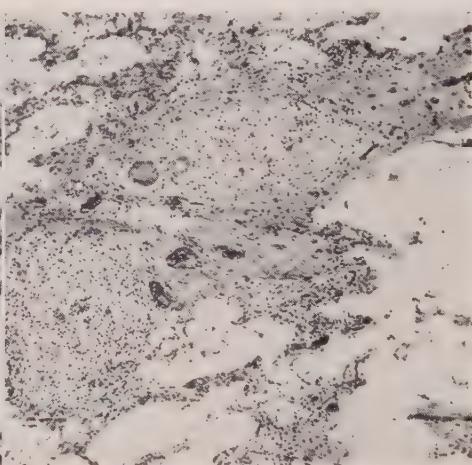


Fig. 115.

pathologic lesion is nonspecific chemical pneumonitis with activation of alveolar macrophages and variable degrees of chronic inflammatory cell infiltration and intra-alveolar edema. Mostly these cases go on to spontaneous remission but sometimes distortion and obliterating fibrosis of lung parenchyma may produce pulmonary insufficiency. Fatal cases have been described^{132, 133} and in some of these there has been transition to lesions found in the chronic form of the disease.

Berylliosis or beryllium granulomatosis, the second type of pulmonary reaction, is a peculiar form of pneumoconiosis which develops

insidiously and is chronic in its course. In our experience¹³⁴ the disease has occurred among workers exposed to fluorescent lamp powder (zinc manganese beryllium silicate) although similar cases have been reported¹³⁵ from inhalation of the oxide or simple salts. The lungs in fatal cases show extensive nodular and irregular fibrosis with marked emphysematous change. Cor pulmonale is characteristically present, and it is apparent that right heart failure has contributed significantly to death. Microscopic examination indicates that the initial lesion is an intra-alveolar collection of phagocytes which soon undergo central necrosis. Foreign body giant cells are prominent in this inflammatory process and occasionally they may be seen to contain or to be in relation to peculiar basophilic bodies, sometimes referred to as "conch shells" (Fig. 114). As the granulomatous lesions expand peripherally they tend to merge with one another, so that widespread areas may become involved (Fig. 115). Concurrent fibroblastic proliferation and resultant scar formation leads to extreme distortion and contraction of contiguous lung tissue. Scarring and hyaline change in a discrete nodule may result in a structure resembling superficially the silicotic nodule; however, whorling and dense hyalinization are not so conspicuous. In contrast to silicosis, complicating tuberculous infection apparently does not occur. The final picture is an extraordinary mixture of active and latent focal and diffuse granulomatous inflammation in combination with dense nodular and irregular fibrosis. Central necrosis may be seen in these lesions, a feature different from silicosis. The tracheobronchial lymph nodes are enlarged and show varying degrees of active inflammation and connective tissue scarring. Nodes completely replaced by fibrous tissue may be encountered. The occurrence of granulomatous lesions in liver and spleen may indicate that the toxic agent or agents are disseminated by the general circulation.

Another prominent feature in berylliosis is severe, diffuse, obliterating pulmonary endarteritis. The resultant decrease in the capacity of the pulmonary vascular bed may be largely responsible for the occurrence of cor pulmonale and ultimate right heart failure.

EXPERIMENTAL.—The intradermal granuloma and the acute pulmonary reaction has been produced experimentally.¹³⁶ The lesion typical of chronic berylliosis has not been duplicated to date. Another experimental finding is the production of bone cancer.^{137, 138}

Organic Compounds

SOLVENTS

Solvents include a large number of volatile liquids which have the common property of being able to dissolve or to become miscible with numerous other substances.^{139, 140, 141} Since vapors or finely dispersed droplets of solvents may contaminate the atmosphere, the lungs are an important portal of entry. Solvents may be miscible with either fat or water, and although they usually possess both characteristics, one or the other frequently predominates. Compounds

which are primarily fat-miscible may be absorbed through the intact skin as well as the lining of the gastrointestinal and respiratory tracts. After absorption, fat-miscible solvents tend to concentrate and to be retained in the tissues that are rich in lipid.

Classification.—The following classes comprise the solvent group: (1) hydrocarbons; (2) halogenated hydrocarbons; (3) alcohols; (4) aldehydes; (5) ketones; (6) ethers; and (7) esters.

General Toxicity of Solvents.—

IMMEDIATELY FATAL NARCOSIS.—The common acute toxic manifestation of solvent poisoning is depression of the central nervous system. Death is caused by terminal medullary paralysis. The pathologic findings are not specific.

DELAYED SYSTEMIC EFFECTS OF ACUTE POISONING.—A single large dose, if not immediately fatal, may lead to degenerative changes in numerous organs, particularly the liver and kidney. The two most important factors in the production of this type of intoxication are the time that the compound is retained in the body and the nature of its catabolic products.

CHRONIC POISONING.—Chronic poisoning is caused by multiple and frequent exposure to



Fig. 116.—Acute pulmonary edema and hemorrhage in aliphatic hydrocarbon poisoning. Death occurred in four hours following accidental ingestion of lighter fluid by child aged 4 years. The lesion is similar to that following inhalation of a gaseous irritant such as oxides of nitrogen.

small doses. Cumulative poisoning, in the sense that it takes place from heavy metals, does not occur. The pathologic manifestations in chronic poisoning may involve the liver, kidney, peripheral and central nervous system, bone marrow, and numerous other organs.

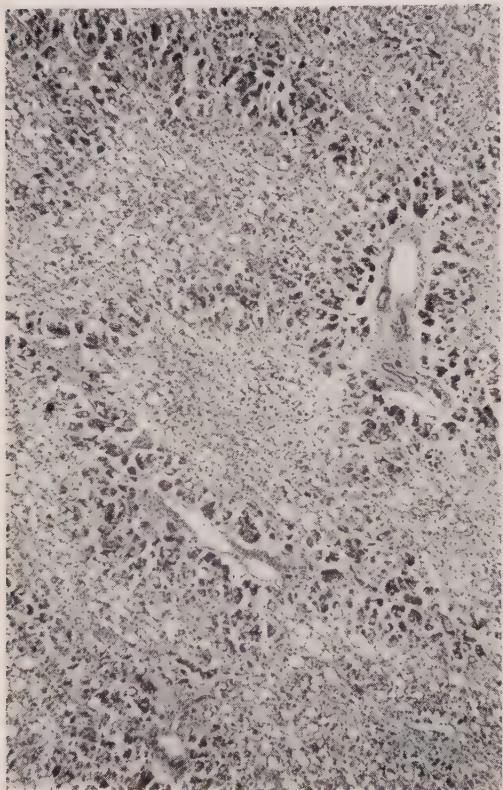


Fig. 117.—Hepatic necrosis in acute carbon tetrachloride poisoning by ingestion. Although all zones are affected, the periphery of the lobules retain recognizable hepatic cells. The central and mid zones are completely destroyed.

Hydrocarbons.—Both aliphatic and aromatic hydrocarbons are obtained by the destructive distillation of coal.

ALIPHATIC HYDROCARBONS.—Of the aliphatic group, gasoline and kerosene are most commonly responsible for poisoning. Whether ingested or inhaled, the absorption of a fatal dose results in depression and convulsive seizures terminating in coma and death. Postmortem examination reveals no characteristic pathologic findings.¹⁴² Severe hemorrhagic pulmonary edema may result from damage of the alveolar capillaries by solvent present in the circulating blood or from aspiration of the ingested hydrocarbon (Fig. 116). Chronic poisoning by the aliphatic hydrocarbons is unusual since these agents are usually excreted rapidly in an unchanged state.

AROMATIC HYDROCARBONS.—The two most important aromatic hydrocarbons are benzene and naphthalene.

CHRONIC BENZENE POISONING.—Chronic intoxication occurs in only a small fraction of those who are exposed daily to benzene vapor. Young adults of the female sex are most susceptible. The characteristic picture is that of pancytopenia. More rarely there may be pure granulopenia or thrombocytopenia. The bone marrow may be hypoplastic or hyperplastic. According to Phillips¹⁴³ the fundamental defect is a failure of maturation of the early undifferentiated cells of the bone marrow. These undifferentiated stem cells may be found in considerable numbers with few or no mature elements in either the hyperplastic or hypoplastic marrow of chronic benzene poisoning.¹⁴⁴ If the condition of leukemia is regarded as an expression of cancer, benzene may be placed into the category of a cancerogenic agent. Occasionally the hematological response to chronic exposure may be myeloid metaplasia, leading, in some instances, to the pathologic picture of true leukemia.

NAPHTHALENE ($C_{10}H_8$).—Naphthalene (naphthol) poisoning occurs principally in children from ingestion of moth balls. The principal manifestation is acute hemolytic anemia.¹⁴⁵ The diagnosis is frequently confused with that of acute hemolytic anemia of Lederer. The hemolytic effect of naphthalene has been confirmed by experimental studies in dogs.¹⁴⁶

Halogenated Hydrocarbons.—The most important compounds in this group are the chlorine derivatives of aliphatic hydrocarbons. These are noninflammable, strongly solvent volatile liquids which are extensively used in industry as degreasers of metals, dry cleansers, fire extinguishers, and solvents for rubber, tar, lacquers, and numerous other substances. Carbon tetrachloride is the typical compound. The unsaturated compounds such as trichlorethylene have been found to be much less toxic. Tetrachlorethane is the most toxic of the common chlorinated hydrocarbons and may cause intravascular hemolysis.

ACUTE POISONING.—Following large doses, death may result from acute narcosis. In light anesthesia with chloroform, death occasionally arises from ventricular fibrillation of the heart.¹⁴⁷ The pathologic findings in this acute type of death are nonspecific.

DELAYED ACUTE POISONING.—A single large dose insufficient to cause fatal depression of the central nervous system may lead to severe visceral damage within the next few days or weeks. The two principal organs affected are the liver and kidneys. In the liver the necrotizing process is located initially in the central portion of the lobule. Death frequently occurs during the yellow or red stage of hepatic injury (Fig. 117). Regeneration proceeds from unaffected cells at the periphery of the lobule.¹⁴⁸ Although a distinct possibility if the patient recovers, complication by obliterating fibrosis is less likely to occur than when necrosis has been initiated by viral and other nonchemical agents. The hepatotoxic mode of action of chlorinated hydrocarbons is not clear. Animals in a good state of protein nutrition can tolerate exposures which likely would be fatal to those in which the pre-existing nutritional state was poor. Methionine and other sulphydryl-containing amino acids protect animals given halogenated hydrocarbons. These experimental re-

sults are not completely translatable to human therapeutics.¹⁴⁹ The hepatotoxic action of chlorinated hydrocarbons is accentuated by the presence of pre-existing liver disease, notably fat metamorphosis.

Methyl Chloride and Methyl Bromide.—These two compounds are gases at ordinary temperatures. Excessive exposure may cause rapidly fatal pulmonary edema. Methyl bromide has an acute vesicant action on the skin.¹⁵⁰ Chronic exposure may lead to encephalopathy and neuropathy.¹⁵¹

Alcohols.—The alcohols act acutely as depressants of the central nervous system. Delayed toxic manifestations depend upon the nature of the partial or complete oxidative products resulting from catabolism of the individual alcohol. Of the three alcohols to be discussed, ethyl alcohol is least toxic since it is oxidized to carbon dioxide and water. On the other hand, methyl alcohol and ethylene glycol are oxidized to formic and oxalic acids, respectively, substances which possess significantly higher toxicity than do the original compounds.

ACUTE ALCOHOL POISONING.—Regardless of the type alcohol ingested, the acute toxic manifestation is depression of the central nervous system, medullary paralysis, and death. During the comatose period, aspiration of gastric contents may lead to acute asphyxia by obstruction of air passages or to acute pulmonary edema by irritation of alveoli from gastric aspiration containing free HCl (see under "anesthetic deaths").

METHYL ALCOHOL.—There is considerable individual variation in susceptibility to this alcohol. After the initial nonspecific period of depression of the central nervous system, delayed manifestations are due to intoxication by formate, the metabolic product of methyl alcohol. The clinical picture may be confused with diabetic acidosis. Amblyopia is characteristic; usually in acute fatal cases the retinal cells exhibit no structural change. Chemical findings are significant only in the sense that positive results indicate absorption of the poison. Treatment should be directed to control of the acidosis.

ETHYL ALCOHOL.—Acute ethyl alcohol poisoning is responsible for a large number of accidental deaths and is, in addition, the predisposing or precipitating factor in numerous others. The pathologic findings in fatal cases are not striking except for an alcoholic odor of tissues. The post-mortem chemical findings depend upon the length of the period of coma which preceded death. If this period is greater than three to four hours, an indeterminate amount of the alcohol that was initially present will have disappeared.¹⁵² Various disease states frequently attributable to alcohol such as hepatic cirrhosis and Wernicke's encephalopathy probably are related to dietary inadequacy rather than to alcohol per se.

ETHYLENE GLYCOL.—Ethylene glycol is widely used in permanent "antifreeze" fluids, and most instances of poisoning result from their ingestion as a substitute for alcohol. Rapidly fatal poisoning results from depression of the central nervous system. The catabolic product, oxalic acid, probably operates as a contributory factor by depressing the blood calcium level. Deaths delayed beyond the first twenty-four hours are re-

lated to the necrotizing effect of oxalic acid upon the renal tubules.^{153, 154} (See Fig. 459, page 576.)

Ethers.—

ETHYL ETHER.—Acute poisoning may follow ingestion or inhalation. Most deaths from ethyl ether poisoning occur incident to its use as an anesthetic agent. Since the mechanisms and pathologic manifestations of acute ethyl ether poisoning do not differ significantly from those of other commonly used anesthetic agents, the ensuing paragraphs concern the general problem of "deaths during anesthesia."

Deaths During Anesthesia.—Deaths that occur during general anesthesia fall into one of two principal categories. In the first, death results from the pre-existing illness or injury that has necessitated the induction of anesthesia, and its coincidence with anesthesia represents a fortuitous rather than a causal relationship. The majority of the so-called "anesthetic" deaths fall in this category. In the second category are included those deaths that are caused by the anesthetic agent.

RAPIDLY FATAL POISONING DUE TO OVERDOSE OF ANESTHETIC AGENT.—The absolute dosage of a volatile anesthetic agent (hydrocarbons, halogenated hydrocarbons, ether) in terms of milligrams inhaled per kilogram of body weight per minute necessary to cause death by depression of the central nervous system is not known. Although substances which are highly volatile are rapidly absorbed, they are also rapidly excreted. Once a level in the blood consistent with the development of surgical anesthesia has been attained, continued inhalation of the anesthetic in properly regulated concentrations merely maintains this level but does not further elevate it. Thus, the formula $C \times T$, in which C is concentration and T is time, is not as reliable an index to total injury as it is with compounds that act as protoplasmic poisons. For example, once surgical anesthesia is established at levels of 130 to 140 mg. per cent ether in the blood, the maintenance of this state may be accomplished by the continued inhalation of the anesthetic vapor in mixtures of 4 vol. per cent concentrations. However, if the concentration is increased to 7 to 10 vol. per cent, the blood ether level rises to 160 to 170 mg. per cent, leading to death by central respiratory failure.¹⁵⁵ The anatomical findings in this type of anesthetic death are not specific and a definite postmortem diagnosis can be made only by chemical examination of the blood.

OTHER MECHANISMS OF DEATH INCIDENT TO THE INDUCTION OF GENERALIZED ANESTHESIA.—Suffocation incident to tongue-swallowing or massive aspiration of gastric contents may lead to rapid asphyxial death. The inhalation of smaller quantities of gastric juice may, after a latent period of several hours, lead to progressively increasing dyspnea and cyanosis from chemical pneumonitis.¹⁵⁶ Death from inhaled gastric juice during the first or second day is caused by hemorrhagic pulmonary edema due primarily to the irritating action of the hydrochloric acid on the alveolar capillaries. If the chemical pneumonitis is survived beyond the

second day, death may result from bronchopneumonia due to the bacterial invasion of the damaged pulmonary parenchyma. The aspiration of other foreign material may lead to pulmonary abscesses or bronchiectasis. A delayed manifestation following anesthesia by halogenated hydrocarbons may be hepatic necrosis.

UNPREDICTABLE ANESTHETIC DEATHS.—At any time during the initiation or maintenance of anesthesia, rapidly fatal death may take place. One type results from so-called "ether convulsions," although this condition may take place during the administration of any anesthetic.¹⁵⁷ The pathogenesis is obscure and the pathologic findings are nonspecific.

Acute deaths during anesthesia may occasionally occur from ventricular fibrillation, cardiac arrest, or acutely developing hypertension or hypotension. Such deaths are more likely to result from the use of particular anesthetics such as the hydrocarbons, halogenated hydrocarbons, and barbiturates. The evidence of pre-existing degenerative or infectious cardiovascular disease and the lack of an otherwise adequate pathologic explanation for death are reasonable grounds for concluding that death has occurred by these mechanisms. Frequently, there are no organic lesions and death must be attributed to an atypical response on the part of cardiorespiratory centers.

DIOXANE.—Dioxane, a cyclic ether, is a colorless, volatile liquid used as a degreaser, a solvent for nitrocellulose, celluloid, oils, and resins, and as a clearing agent in histologic procedures. Locally, dioxane is irritating to the respiratory tract. Following prolonged exposure, dioxane is necrotizing to the renal tubules and the liver.¹⁵⁸ In the fatal cases reported in human beings, the renal lesions were responsible primarily for death.¹⁵⁹

AROMATIC NITRO AND AMINO COMPOUNDS

These compounds are used extensively in organic synthesis, particularly in the manufacture of dyes and explosives. The principal portals of entry are the gastrointestinal tract and the skin. Dangerous poisoning by inhalation is uncommon because most of the compounds in this group have limited volatility.

Manifestations of Intoxication.—

ACUTE POISONING.—Acute poisoning may be manifested by any combination of the following four forms:

1. Central nervous system depression. Large doses give rise to rapidly ensuing coma and death, usually associated with convulsive seizures. There are no specific pathologic findings.

2. Acute hemolysis. The hemolytic reaction may lead to rapid death. The delayed effects are due to renal insufficiency. The renal lesion may be hemoglobinuria or lower nephron nephrosis.

3. Methemoglobin formation. The production of methemoglobin probably occurs incident to the formation of phenylhydroxylamine, which seems to be a catabolic product common to most of these agents.^{160, 161} Sulfhemoglobin is also said to be formed following exposure to members of this group.¹⁶²

4. Acute parenchymatous degeneration. Systemic lesions may occur in any location if the period of survival extends beyond the initial period of acute collapse.

CHRONIC INTOXICATION.—Of the varying manifestations of chronic toxicity, methemoglobinemia, encephalopathy, peripheral neuropathy, anemia, hepatic necrosis, and dermatitis are those which most commonly occur. Continued exposure may lead to papillomatosis of the urinary bladder and finally to malignant degeneration at this site.¹⁶³

Nitrobenzene.—Any of the group manifestations of acute toxicity may be seen following exposure to nitrobenzene. The compound, an oily liquid, may lead to profound collapse and rapid death when splashed upon the clothes. Following ingestion, rapid death may occur.¹⁶⁴ At postmortem examination, the odor of shoe polish (nitrobenzene) may be detected. The color of blood and tissues may be chocolate-brown. Acute nonfatal poisoning, manifested principally by methemoglobinemia, has been reported following the wearing of shoes to which a nitrobenzene dye had been freshly applied.¹⁶⁵ Methemoglobinemia, mild to moderate anemia, polyneuropathy, nervousness, headache, and visual disturbances are manifestations of chronic intoxication.

Aniline.—The toxic action of aniline is similar to but not as severe as that of nitrobenzene. The most common manifestation of poisoning is methemoglobinemia.¹⁶⁶ Large doses may lead to hemolysis and depression of the central nervous system. Methemoglobinemia following the absorption of aniline from diapers stamped with aniline ink has been reported in infants.¹⁶⁷

Dinitrophenol.—Dinitrophenol speeds oxidation. Although the increase in metabolism is not accompanied by profound circulatory disturbances, the body temperature may be significantly elevated. Large doses lead to death by acute hyperthermia. With the exception of yellow staining of body tissues and fluids, there are no significant pathologic findings.¹⁶⁸ Exfoliative dermatitis, cataracts, and granulopenia have followed the continued use of dinitrophenol as a weight reducer.

HYPNOTIC DRUGS

The common toxic action of this group of chemically miscellaneous compounds is to produce irregularly descending paralysis of the cerebrospinal axis and finally death from central respiratory and circulatory failure.¹⁵⁵ Most cases of poisoning in man are acute and occur principally from ingestion and occasionally from injection. There are no characteristic pathologic findings.

Barbiturates.—Protracted coma of twenty-four to forty-eight hours or more depending upon whether the barbiturate is rapidly acting or slowly acting is the principal manifestation in acute barbiturate poisoning. During the terminal period, oliguria or anuria may develop incident to vasoconstrictor collapse and renal anoxia. The pathologic changes in the kidneys are mild degenerative changes in the tubular epithelium. Delayed deaths may be caused by bronchopneumonia. Some of the strongly alkaline bar-

biturate salts, e.g., Seconal Sodium, may give rise to local gastric injury. People who recover may develop nervous system lesions if the anoxia to which they were subjected had been sufficiently prolonged and severe. The combined administration of a barbiturate and ethyl alcohol leads to cumulative effects.¹⁶⁹ Blood levels in fatal barbiturate poisoning vary depending upon the length of survival and the type of barbiturate (3 to 20 mg. per cent). We have seen delayed deaths in which postmortem blood was barbiturate-free. Ingestion of large amounts of a rapidly acting barbiturate (Seconal or Nembutal) may cause a rapid death within an hour or two.

Morphine.—The period of coma which precedes death usually is less than that in barbiturate poisoning and ordinarily does not exceed twenty-four hours. Except for the presence of an acrid odor in the case of poisoning by the crude opium alkaloid, the postmortem examination reveals no significant findings. The person who is addicted to morphine may tolerate many times the usual lethal dose of 2 to 3 grains.

Chloral Hydrate and Paraldehyde.—In only rare instances is chloral hydrate or paraldehyde responsible for fatal poisoning. Chloral hydrate and ethyl alcohol may be cumulative in their effect.

ANALGESICS AND ANTIPYRETICS

Although the members of this group have similar pharmacologic properties, their toxic action varies widely.

Salicylates.—Fatal acute salicylate poisoning may occur following a single excessively large dose or from repeated small doses incident to treatment. The primary toxic manifestations are due to stimulation of the respiratory center leading to alkaloisis.¹⁷⁰ In the event that death does not take place rapidly, there may be a tendency toward the development of secondary acidosis because of glycogen depletion and resulting incomplete oxidation of fat. Another manifestation of salicylate intoxication is depression of the prothrombin blood level.¹⁷¹ This effect probably is due to the fact that salicylate is a chemical analogue of vitamin K. The postmortem findings are not characteristic but the presence of focal serous and intraparenchymal hemorrhage is suggestive of salicylate poisoning.

Cinchophen.—The chief toxic manifestation of cinchophen poisoning is hepatic necrosis.¹⁷² The occurrence of the lesion is an unpredictable event which is unrelated to the size of the dose or to previous medication.

Acetanilid and Acetphenetidin.—Acetanilid and acetphenetidin are derivatives of aniline. The principal manifestations of intoxication is methemoglobinemia. Large doses may have an acute hemolytic effect¹⁷³ or may lead to death by acute methemoglobin anoxia. Acetanilid has been reported to cause sulfhemoglobinemia.¹⁷⁴

Aminopyrine and Antipyrine.—Upon rare occasions, possibly because of personal idiosyncrasy or the development of hyperergy, the use of aminopyrine or antipyrine may give rise to severe relative or absolute granulopenia.^{175, 176} In contradistinction to other chemicals (ben-

zene, sulfonamides, trinitrotoluene, and many others) which irregularly depress the formation of red cells, neutrophiles, or platelets in unpredictable combinations, these compounds selectively interfere with granulocytic maturation. Histologic studies of the bone marrow show maturation arrest at the myeloblastic stage.¹⁷⁷ There is no anemia or thrombopenia. The most characteristic clinical manifestation of the disease is an acute necrotizing inflammation of the upper air passages. The infection is caused by organisms normally present there and apparently occurs because of the loss of protection usually provided by the polymorphonuclear leukocytes. Frequently, there is an associated bronchopneumonia. The exudative reaction is characterized by the absence of neutrophiles.

ALKALOIDS AND GLUCOSIDES

These groups include a number of complex organic compounds, many of which are used therapeutically and most of which are highly toxic in excessive doses. Although they are capable of inducing widely diversified physiologic disturbances, most of them fail to produce characteristic acute or chronic pathologic changes even though they have been responsible for death. Postmortem recognition that death was due to poisoning by an alkaloid or glucoside depends upon the toxicologic findings rather than upon the gross or microscopic changes.

In animals, digitalis poisoning may result in focal myocardial necrosis.¹⁷⁸ Chronic ergot poisoning in man may lead to bilaterally symmetrical gangrene of the extremities.¹⁷⁹

ESSENTIAL OILS

The essential or ethereal oils are volatile, odorous plant constituents of a widely varying nature. The group includes camphor, menthol, turpentine, the oils of savin, rue, tansy, pennyroyal, thymol, absinthe, eucalyptus, wintergreen (methyl salicylate), and others. Ingestion of methyl salicylate ointment is a frequent cause for poisoning. According to Starkenstein,² the essential oils may act as severe systemic poisons, and as local irritants at the portal of entry or of excretion.

Fatal acute poisoning may occur following accidental or suicidal ingestion or following attempts to induce abortion by a single large or repeated small doses. Other than for the odor of the oil, there are no characteristic gross or microscopic pathologic findings.

Many abortifacient pastes and gels contain essential oils as ingredients. The intrauterine injection of these preparations may lead to local tissue destruction or to rapid death from systemic injury. In the latter case, the principal lesion may be severe hemorrhagic pulmonary edema. Whether the responsible factor is the oil itself or another constituent is problematic.

Miscellaneous

Thiouracil.—An analysis of 5,745 patients treated with thiouracil for thyrotoxicosis indicates that the most frequently occurring toxic reactions were granulopenia, drug fever, and

dermatitis.¹⁸⁰ The most serious of these complications was granulopenia, which occurred in 142, or 2.5 per cent, of the cases and resulted in 21 deaths from agranulocytosis. The lesion is arrest of maturation at the myeloblastic stage (see under amidopyrine). Of the various factors concerned in the production of these neutropenic reactions, that of hypersensitivity is regarded to be most important.¹⁸¹ The effect on the thyroid is described on page 996.

Mushroom Poisoning.—The principal poisonous mushrooms are *Amanita phalloides* and *Amanita muscaria*. In poisoning by the former, there is a latent period of several hours before the initial symptoms of gastrointestinal irritation begin. Death may be delayed for several days. The principal pathologic lesions are hepatic necrosis and degeneration and necrosis in the proximal tubular epithelium of the kidneys.^{182, 183} Widespread fatty degeneration may be encountered in many organs, including the heart¹⁸⁴ and brain. Acute hemolysis may be another manifestation of poisoning by this variety of mushroom.¹⁸⁵

The poisonous substance in *Amanita muscaria* is muscarine, an alkaloid of the pilocarpine series. In the event of fatal intoxication, death occurs within a few hours after ingestion. There are no characteristic pathologic findings.

Venoms.—The sting or bite of jellyfish, bees, scorpions, spiders, and snakes may be poisonous to man.¹⁸⁶ Although the poisoning factors have been incompletely identified, there is some evidence that many of these toxic agents are associated with a protein fraction. The systemic toxic manifestations may include a neurotoxic, a hemolytic, or a vasculotoxic effect, or any combination of these. The nature and extent of the local inflammatory reaction at the site of the bite or sting is variable.

Pesticides.—A result of World War II has been the discovery of synthetic organic compounds which combine relatively low cost with powerful insecticidal or rodenticidal activity. Many of these substances in use may be extremely hazardous. Dangerous amounts may be absorbed through the skin and lungs as well as by ingestion. DDT and other complex chlorinated hydrocarbons are potent insecticides. In large amounts these compounds are toxic to the nervous system. Subacute doses have the usual hepatotoxic and nephrotoxic effects common to chlorinated hydrocarbons. The greatest body of information has accumulated in the case of DDT. Most cases of acute poisoning probably have been due in large part to ingestion of the solvent employed (e.g., kerosene). The non-fatal toxic effects of DDT are said to include anorexia, nervousness, muscular weakness, tremors and other manifestations of nervous and systemic injury.^{187, 188, 189} Hepatic damage has been reported following prolonged administration of very small amounts of DDT (5 ppm) in experimental animals,¹⁹⁰ an amount which may be no greater than that which could be encountered by workers in this field. Chlordane, Toxaphene, and Gammexane (benzene hexachloride) give rise to toxic manifestations resembling those due to DDT.¹⁹¹

Another group of potent insecticidal agents are organic phosphorus compounds (see section on war gases).

The two new principal rodenticides are fluoracetates and ANTU. Sodium fluoracetate (1080), an enzyme inhibitor, is specifically toxic to black rats.^{192, 193} ANTU (alphanaphthyl-thiourea) is lethal to the Norway strain of rat and kills by the production of acute pulmonary edema.^{194, 195} A recent new approach to rat extermination is use of a Dicumarol compound. In the event that human ingestion occurs, specific treatment is available by administration of vitamin K.

References

- Gonzales, T. A., Vance, M., and Helpern, M.: Legal Medicine and Toxicology, New York, 1940, D. Appleton-Century Co., Inc.
- Starkenstein, E., Rost, E., and Pohl, J.: Toxikologie, Berlin, 1929, Urban und Schwarzenberg.
- Petri, E.: Handbuch der speziellen pathologischen Anatomie und Histologie, vol. X, Berlin, 1930, Julius Springer.
- Freidenwald, J. S., Hughes, W. F., and Herman, H.: Arch. Ophth. 35: 98, 1946; 31: 279, 1944 (acid burns of the eye.)
- Leegaard, T.: J. Laryngol. & Otol. 60: 389, 1945 (corrosive injuries of the esophagus).
- Stumboff, A. V.: Arch. Otolaryngol. 52: 419, 1950 (chemical burns of the oral cavity and esophagus).
- Flack, A. N., and Scofield, P. D.: Indust. Med. 16: 17, 1947 (hydrofluoric acid burn).
- Jeghers, H., and Murphy, R.: New England J. Med. 233: 208, 1945 (oxalate metabolism).
- Dunn, J. S., Haworth, A., and Jones, N. A.: J. Path. & Bact. 27: 299, 1924 (oxalate nephritis).
- Hamilton, A.: Industrial Poisons in the United States, New York, 1925, The Macmillan Company.
- Zeidman, I., and Dentl, R.: Am. J. M. Sc. 210: 328, 1945 (poisoning by hydroquinone and monoethyl-p-aminophenol sulfate).
- Sterner, J. H., Oglesby, F. L., and Anderson, B.: J. Indust. Hyg. & Toxicol. 29: 60, 1947 (quinone vapors and their harmful effects).
- Goldberg, S. E.: Arch. Int. Med. 43: 196, 1929 (ochronosis).
- Kline, B. S.: Arch. Int. Med. 36: 220, 1925 (formaldehyde poisoning).
- Jetter, W. W., and Hunter, F. T.: New England J. Med. 240: 794, 1949 (death from attempted abortion with KMnO₄ douche).
- Gordon, S., and Brown, J. A. H.: Lancet 2: 503, 1947 (KClO₄ poisoning).
- McDonough, J. F.: New England J. Med. 232: 189, 1945 (vaginal bleeding from KMnO₄ as abortifacient).
- Jetter, W. W.: Unpublished data.
- Wells, D. B., Humphrey, H. D., and Coll, J. J.: New England J. Med. 226: 629, 1942 (tannic acid).
- Hartman, F. W., and Romence, H. L.: Ann. Surg. 118: 402, 1943 (liver necrosis in burns).
- Colhuquon, K. G.: M. J. Australia 2: 652, 1928 (picric acid).
- Dennie, C. C., McBride, W. L., and Davis, P. E.: Arch. Dermat. & Syph. 20: 698, 1929 (picric acid).
- Harris, A. H., Binkley, O. F., and Chenoweth, B. M., Jr.: Am. J. Pub. Health 36: 727, 1946 (hematuria due to picric acid poisoning).
- Henderson, Y., and Haggard, H. W.: Noxious Gases, ed. 2, New York, 1943, Reinhold Publishing Corp.
- Moritz, A. R.: Personal communication.
- Baitzer, A. M.: J. Indust. Hyg. & Toxicol. 32: 400, 1950 (chronic exposure to air pollutants and acute infectious disease).
- Hicks, S. P.: Arch. Path. 49: 111, 1950 (brain metabolism in vivo I).
- Morrison, L. R.: Arch. Neurol. & Psychiat. 55: 1, 1946 (histopathologic effect of anoxia on central nervous system).
- Hardy, H. L., and others: New England J. Med. 242: 968, 1950 (thiocyanate effect following exposure).

30. Hunter, D.: *Industrial Toxicology*, New York and London, 1944, Oxford University Press.
31. Lucké, B.: *Mil. Surgeon* 99: 371, 1946 (lower nephron nephrosis).
32. McDonald, J. M., and McIntosh, A. P.: *Arch. Indust. Hyg. & Occup. Med.* 3: 445, 1951 (fatalities from hydrogen sulfide in wells).
33. Cameron, R. G., Carleton, H. M., and Short, R. H. D.: *J. Path. & Bact.* 58: 411, 1946 (lewisite and allied compounds).
34. Jacobson, L. O., Spurr, C. L., Barron, E. S. G., Smith, T., Lusbaugh, C., and Dick, G. F.: *J. A. M. A.* 132: 263, 1946 (nitrogen mustard therapy).
35. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and McLean, M. T.: *J. A. M. A.* 132: 126, 1946 (nitrogen mustard therapy).
36. Griffin, A. C., Brandt, E. L., and Tatum, E. L.: *J. A. M. A.* 144: 571, 1950 (nitrogen mustard as cancer-inducing agents).
37. Wood, J. R.: *J. A. M. A.* 144: 606, 1950 (chemical warfare).
38. Wood, J. R.: *J. A. M. A.* 145: 1264, 1951 (chemical defense).
39. Grob, D., Lilienthal, J. L., Jr., Harvey, A. M., and Jones, B. F.: *Bull. Johns Hopkins Hosp.* 81: 217, 1947 (systemic effects of diisopropyl fluorophosphate in man).
40. Dubois, K. P., and others: *J. Pharmacol. & Exper. Therap.* 95: 79, 1949 (toxicity and mechanism of action of parathion).
41. Grob, D., and others: *Ann. Int. Med.* 31: 899, 1949 (death due to parathion and anticholinesterase insecticide).
42. Randall, R. V., and Seeler, A. O.: *New England J. Med.* 289: 1004, 1949 (BAL).
43. Sexton, G. B., and Gowdy, C. W.: *Arch. Dermat. & Syph.* 56: 634, 1947 (relation between thiamine and arsenical toxicity).
44. Ecker, A. D., and Kernohan, J. W.: *Arch. Neurol. & Psychiat.* 45: 24, 1941 (arsenic as possible cause of subacute encephalomyelitis).
45. Globus, J. H., and Ginsberg, S. W.: *Arch. Neurol. & Psychiat.* 30: 1226, 1933 (arsphenamine encephalitis).
46. McCarthy, L.: *Histopathology of Skin Diseases*, St. Louis, 1931, The C. V. Mosby Co.
47. O'Leary, P. A., Snell, A. M., and Bannick, E. G.: *J. A. M. A.* 90: 1856, 1928 (portal cirrhosis associated with arsenical poisoning).
48. Cannon, A. B.: *New York State J. Med.* 36: 219, 1936 (chronic arsenical poisoning).
49. Scott, V., Maxwell, R. W., and Skinner, J. S.: *J. A. M. A.* 139: 217, 1949 (Jarisch-Herxheimer phenomenon).
50. Hahn, R. D.: *Am. J. Syph., Gonor. & Ven. Dis.* 25: 659, 1941 (fatal reactions in anti-syphilitic treatment).
51. Eagle, H., and Magnuson, H. J.: *Am. J. Syph., Gonor. & Ven. Dis.* 30: 420, 1946 (arsenic poisoning).
52. Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, 1942, Lea & Febiger.
53. Keall, J. H. H., Martin, N. H., and Tunbridge, R. E.: *Brit. J. Indust. Med.* 3: 175, 1946 (poisoning by sodium tellurite).
54. DeMaio, R. H., and Jetter, W. W.: *J. Indust. Hyg. & Toxicol.* 30: 53, 1948 (tellurium).
55. Moxon, A. L., and Rhanian, M.: *Physiol. Rev.* 23: 305, 1943 (selenium poisoning).
56. Cooper, G., Jr.: *Am. J. Roentgenol.* 58: 129, 1947 (inhalation lead poisoning).
57. Hamilton, A.: *Industrial Toxicology*, New York, 1934, Harper & Brothers.
58. Belknap, E. L.: *J. A. M. A.* 139: 818, 1949 (lead poisoning).
59. Wachstein, M.: *Arch. Path.* 48: 442, 1949 (lead poisoning).
60. Wachstein, M.: *Am. J. Clin. Path.* 19: 608, 1949 (acid-fastness of nuclear inclusion bodies that are induced by ingestion of lead and bismuth).
61. Jones, R. R.: *J. A. M. A.* 104: 195, 1935 (plumbism).
62. Drinker, P.: *Occup. Med.* 3: 145, 1947 (public exposure to lead).
63. Wormser, F. E.: *Occup. Med.* 3: 135, 1947 (exposure to lead).
64. Cotter, L. H.: *J. Indust. Hyg. & Toxicol.* 28: 44, 1946 (lead intoxication by inhalation).
65. Castrop, V. J.: *Indust. Med.* 17: 59, 1948 (urinary and blood leads).
66. Patty, F. A.: *Indust. Med.* 18: 368, 1949 (lead in biological fluids).
67. Akelatis, A. J.: *J. Nerv. & Ment. Dis.* 93: 313, 1941 (lead encephalopathy).
68. Ennis, J. M., and Harrison, H. E.: *Pediatrics* 5: 853, 1950 (treatment of lead encephalopathy).
69. Byers, R. K., and Lord, E. E.: *Am. J. Dis. Child.* 66: 471, 1943 (late effects of lead poisoning on mental development).
70. Reznikoff, P., and Aub, J. C.: *Arch. Neurol. & Psychiat.* 17: 444, 1927 (lead palsies).
71. Machle, W.: *Occup. Med.* 3: 150, 1947 (hematologic changes in lead absorption and lead poisoning).
72. Yeager, C. F.: *Connecticut M. J.* 12: 710, 1948 (chronic lead absorption and poisoning).
73. Norris, C., and Gettier, A. O.: *J. A. M. A.* 85: 818, 1925 (tetraethyl lead poisoning).
74. Cassells, D. A. K., and Dodds, E. C.: *Brit. Med. J.* 2: 681, 1946 (tetraethyl lead poisoning).
75. Ray, C. T., and Burch, G. E.: *Am. J. M. Sc.* 217: 96, 1949 (mercurial diuretics).
76. Edwards, J. B.: *Am. J. Path.* 18: 1101, 1942 (mercury).
77. Harmon, E. L.: *Am. J. Path.* 4: 321, 1938 (mercury).
78. Neal, P. A.: *Am. J. Pub. Health* 28: 907, 1938 (mercury).
79. Neal, P. A., and others: *Pub. Health Bull.* 263: 1, 1941 (mercurialism and its control in the felt-hat industry).
80. Lewis, L.: *J. A. M. A.* 129: 123, 1945 (mercury poisoning).
81. Hill, W. H.: *Canad. Pub. Health J.* 34: 158, 1943 (mercury poisoning).
82. Hunter, D., Bomford, R. R., and Russell, D. S.: *Quart. J. Med.* 9: 193, 1940 (mercury poisoning).
83. Mayer, L., and Baehr, G.: *Surg. Gynec. & Obst.* 15: 309, 1912 (bismuth poisoning).
84. Pappenheimer, A. M., and Maechling, E. H.: *Am. J. Path.* 10: 577, 1934 (inclusion in renal epithelium cells following use of certain bismuth preparations).
85. Wallace, W. M.: *J. A. M. A.* 133: 1280, 1947 (bismuth subnitrate).
86. Tepperman, J., Marquerdt, R., Reifenstein, G., and Lozner, E.: *J. A. M. A.* 146: 923, 1951 (methemoglobin cyanosis).
87. Finch, Clement A.: *New England J. Med.* 239: 470, 1948 (methemoglobinemia and sulfhemoglobinemia).
88. Cohen, A., Goldman, J., and Dubbs, A. W.: *J. A. M. A.* 133: 749, 1947 (gold and arsenic poisoning).
89. Marriott, H. J. L., and Peters, H. R.: *Ann. Int. Med.* 32: 864, 1950 (blood dyscrasias secondary to gold).
90. Lockie, L. M., Norcross, B. M., and George, C. W.: *J. A. M. A.* 133: 754, 1947 (treatment of two reactions due to gold).
91. Ragan, C., and Boots, R.: *J. A. M. A.* 133: 752, 1947 (treatment of gold dermatitis).
92. Archer, B. H.: *J. A. M. A.* 144: 782, 1950 (hepatitis following gold therapy).
93. Doyle, J. B., and Cannon, E. F.: *Ann. Int. Med.* 33: 1468, 1950 (polyneuritis following gold therapy).
94. Snyder, R. G., Traeger, C. H., and Squires, W. H.: *Indust. Med.* 11: 425, 1942 (gold therapy).
95. Heyroth, F. F.: *Pub. Health Rep., Supp.* 197, 1947 (thallium).
96. Munch, J. C.: *J. A. M. A.* 102: 1929, 1934 (thallatoxicosis).
97. Gettier, A. O., and Weiss, L.: *Am. J. Clin. Path.* 13: 422, 1943 (thallium poisoning).
98. Canavan, M., Cobb, S., and Drinker, C. K.: *Arch. Neurol. & Psychiat.* 32: 501, 1934 (manganese poisoning).
99. Chretien, T. E.: *New England J. Med.* 232: 247, 1945 (acute phosphorus poisoning).
100. Rubitsky, H. J., and Myerson, R. M.: *Arch. Int. Med.* 83: 164, 1949 (acute phosphorus poisoning).
101. Wertham, F.: *Arch. Neurol. & Psychiat.* 28: 320, 1932 (acute phosphorus poisoning).
102. Blumenthal, S., and Lesser, A.: *Am. J. Dis. Child.* 55: 1280, 1938 (acute phosphorus poisoning).

103. Adams, C. O., and Sarnat, B. G.: Arch. Path. 30: 1192, 1940 (phosphorus poisoning).
104. Heimann, H.: J. Indust. Hyg. & Toxicol. 28: 142, 1946 (phosphorus poisoning).
105. Mallory, F. B.: Am. J. Path. 9: 557, 1933 (phosphorus and alcoholic cirrhosis).
106. Ashburn, L. L., McQueeny, A. J., and Faulkner, R. R.: Proc. Soc. Exper. Biol. & Med. 67: 351, 1948 (chronic phosphorus poisoning).
107. Pharmacology and Toxicology of Uranium Compounds, Div. VI: Vols. I and II, ed. 1, New York, 1949, McGraw-Hill Book Co.
108. Hunter, W. C., and Roberts, J. M.: Am. J. Path. 9: 133, 1933 (effects of potassium bichromate).
109. Sanders, J. E., and Camp, C. D.: Am. J. M. Sc. 198: 551, 1939 (chromium poisoning).
110. Jetter, W. W., and Lind, H.: Unpublished data.
111. Vaccaro, L.: Indust. Med. 10: 246, 1941 (chromium poisoning).
112. Mackle, W., and Gregorius, F.: Pub. Health Rep. 63: 1114, 1948 (cancer of respiratory system in U. S. chromate-producing industries).
113. Corcoran, A. C., Taylor, R. D., and Page, I. H.: J. A. M. A. 139: 685, 1949 (lithium poisoning).
114. Hanlon, L. W., and others: J. A. M. A. 139: 688, 1949 (lithium chloride).
115. Masson, G.: Addendum, J. A. M. A. 139: 688, 1949.
116. Nesbit, R. M.: Surg., Gynec. & Obst. 80: 651, 1945 (boric acid).
117. McNally, W. D., and Rust, C. A.: J. A. M. A. 90: 382, 1928 (boric acid poisoning).
118. Pfeiffer, C. C., Hallman, L. F., and Gersh, I.: J. A. M. A. 128: 266, 1945 (boric acid ointment).
119. Fellows, A. W., Campbell, J. J., and Wadsworth, R. C.: Maine M. A. J. 39: 339, 1948 (boric acid poisoning).
120. Fisher, R. S.: Am. J. Path. 27: 745, 1951 (boric acid poisoning).
121. Lidbeck, W. L., Hill, L. B., and Beeman, J. A.: J. A. M. A. 121: 826, 1943 (sodium fluoride poisoning).
122. Rabinowitz, I. M.: Canad. M. A. J. 52: 345, 1945 (fluoride poisoning).
123. Peters, J. H.: Am. J. M. Sc. 216: 278, 1948 (therapy of acute fluoride poisoning).
124. Roholm, K.: Fluorine Intoxication, London, 1937, H. K. Lewis & Co., Ltd.
125. Larner, J.: Indust. Med. 19: 535, 1950 (toxicological and metabolic effects of fluorine-containing compounds).
126. Badger, D. C.: Am. J. Dis. Child. 78: 72, 1949 (toxic level of fluorine in water supplies).
127. Hasterlik, R. J.: Arch. Indust. Hyg. & Occup. Med. 3: 547, 1951 (chronic beryllium poisoning).
128. Sterner, J. H., and Eisenbud, M.: Arch. Indust. Hyg. & Occup. Med. 4: 123, 1951 (beryllium intoxication).
129. Large, H. D., Jr., and Stumpe, A. R.: South. Med. J. 44: 36, 1951 (cutaneous beryllium granuloma).
130. Gerrie, J., Kennedy, F., and Richardson, S. L.: Canad. M. A. J. 62: 529, 1950 (beryllium granulomatosis).
131. Grier, R. S., Nash, P., and Friedman, D. G.: J. Indust. Hyg. & Toxicol. 30: 228, 1948 (skin lesions in persons exposed to beryllium compounds).
132. Van Ostrand, N. S., Hughes, R., DeNardi, J. M., and Carmody, M. G.: J. A. M. A. 129: 1084, 1945 (beryllium poisoning).
133. Dutra, F. R.: Am. J. Path. 24: 1137, 1948 (beryllium pneumonitis and granulomatosis).
134. Jetter, W. W.: Am. J. Path. 24: 690, 1948 (beryllium pneumoconiosis).
135. Dutra, F. R.: Arch. Indust. Hyg. & Occup. Med. 3: 81, 1951 (beryllium granulomas of skin).
136. Stokinger, H. E., and others: Arch. Indust. Hyg. & Occup. Med. 1: 379, 1950 (acute inhalation toxicity of beryllium).
137. Dutra, F. R., Largent, E. J., and Roth, J. J.: Arch. Path. 51: 473, 1951 (osteogenic sarcoma after inhalation of beryllium oxide).
138. Dutra, F. R., and Largent, E. J.: Am. J. Path. 26: 197, 1950 (osteosarcoma induced by beryllium oxide).
139. Clinton, M., Jr.: New England J. Med. 238: 51, 1948 (poisoning by volatile solvents).
140. Wilson, R. H.: J. A. M. A. 139: 906, 1949 (industrial solvent poisoning).
141. Foulger, J. H.: J. A. M. A. 139: 826, 1949 (physiological effects of industrial solvents).
142. Machle, W.: J. A. M. A. 117: 1965, 1941 (gasoline intoxication).
143. Phillips, D. L.: J. Bowman Gray School Med. 3: 191, 1945 (benzene and its derivatives).
144. Mallory, T. B., Gall, E. A., and Erickley, W. J.: J. Indust. Hyg. & Toxicol. 21: 355, 1939 (benzene).
145. Abelson, S. M., and Henderson, A. T.: U. S. Armed Forces M. J. 2: 491, 1951 (moth ball poisoning).
146. Zuelzer, W. W., and Apt, L.: J. A. M. A. 141: 185, 1949 (naphthalene poisoning).
147. Geiger, A. J.: J. A. M. A. 123: 141, 1943 (chlorinated hydrocarbons).
148. Himsworth, H. P.: Lectures on the Liver and Its Diseases, Cambridge, 1947, Harvard University Press.
149. Miller, L. L.: Occup. Med. 5: 194, 1948 (toxicity of halogenated hydrocarbons).
150. Gray, P. H. K.: J. Roy. Nav. M. Serv. 30: 214, 1944 (methyl bromide).
151. DeJong, R.: J. A. M. A. 125: 702, 1944 (methyl bromide).
152. Jetter, W. W.: Clinics 1: 1487, 1943 (acute alcoholism).
153. Miles, G.: Arch. Path. 41: 631, 1947 (ethylene glycol poisoning).
154. Smith, D.: Arch. Path. 51: 423, 1951 (acute and subacute ethylene glycol poisoning).
155. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Company.
156. Mendelson, C. L.: Am. J. Obst. & Gynec. 41: 191, 1946 (anesthesia).
157. Simpson, E. E.: New England J. Med. 232: 160, 1945 (anesthesia).
158. Fairley, A., Linton, E. C., and Ford-Moore, H.: J. Hyg. 34: 486, 1934 (dioxane).
159. Barber, H.: Guy's Hosp. Rep. 84: 267, 1934 (dioxane).
160. Brodie, B. B., and Axelrod, J.: J. Pharmacol. & Exper. Therap. 94: 29, 1948 (acetanilid).
161. Brodie, B. B., and Axelrod, J.: J. Pharmacol. Exper. Therap. 97: 1, 1949 (acetophenetidin).
162. Lazarus, S.: Brit. M. J. 2: 565, 1945 (sulfhemoglobinemia due to aniline derivatives).
163. Hueper, W. C., Wiley, F. H., and Wolfe, H. D.: J. Indust. Hyg. & Toxicol. 20: 46, 1938 (beta-naphthylamine).
164. Chamber, J. V., and O'Neill, F. J.: U. S. Nav. M. Bull. 44: 1112, 1945 (nitrobenzene poisoning).
165. Stifel, R. E.: J. A. M. A. 72: 395, 1919 (poisoning by shoe dye).
166. Clark, B. B., Van Loon, E. J., and Morrissey, R. W.: J. Indust. Hyg. & Toxicol. 25: 1, 1943 (aniline poisoning).
167. Graubart, J., Bloom, C. J., Coleman, J. C., and Solomon, H. N.: J. A. M. A. 128: 1155, 1945 (dye poisoning).
168. Purvine, K.: J. A. M. A. 107: 2046, 1936 (sodium dinitrophenol).
169. Jetter, W. W., and McLean, R.: Arch. Path. 36: 112, 1943 (synergistic effect of phenobarbital and ethyl alcohol).
170. Ryder, H. W., Shaver, M., and Ferris, E. B.: New England J. Med. 232: 617, 1945 (salicylism).
171. Meyer, O., and Howard, B.: Proc. Soc. Exper. Biol. & Med. 53: 234, 1943 (salicylates).
172. Lenzner, A. R., Lockie, M., and Becker, C. F.: New England J. Med. 236: 500, 1947 (cinchophen).
173. Van Loon, E. J., and Clark, B. B.: J. Lab. & Clin. Med. 29: 942, 1944 (acetanilid and acetophenetidin).
174. Morgan, T. N., and Anderson, A. G.: Brit. M. J. 2: 187, 1940 (acetanilid poisoning).
175. Kracke, R. R.: J. A. M. A. 111: 1255, 1938 (relation of drug therapy to neutropenic states).
176. Fitz-Hugh, T.: J. A. M. A. 111: 1643, 1938 (agranulocytosis).
177. Darling, R. C., Parker, F., and Jackson, H.: Am. J. Path. 12: 1, 1936 (agranulocytosis).

178. LaDue, J. S.: *J. Pharmacol. & Exper. Therap.* **76**: 1, 1942 (digitalis poisoning).
179. Yater, W. M., and Cahill, J. A.: *J. A. M. A.* **106**: 1625, 1936 (ergot poisoning).
180. Winkle, W. V., and others: *J. A. M. A.* **130**: 343, 1946 (thiouracil).
181. Lesses, M. F., and Gargin, S. L.: *New England J. Med.* **233**: 803, 1945.
182. Vander Veer, J. B., and Farley, D. L.: *Arch. Int. Med.* **55**: 773, 1935 (mushroom poisoning).
183. Dubash, J., and Teare, D.: *Brit. M. J.* **1**: 45, 1946 (mushroom poisoning).
184. Hyman, A. S.: *Bull. Johns Hopkins Hosp.* **42**: 8, 1928 (mushroom poisoning).
185. Hoechstetter, S. S.: *M. Bull. Vet. Admin.* **20**: 58, 1942 (food poisoning).
186. Essex, H. E.: *Physiol. Rev.* **25**: 148, 1945.
187. Wigglesworth, V. B.: *Brit. M. J.* **1**: 517, 1945 (DDT).
188. Mackerras, I. M., and West, R. F. K.: *M. J. Australia* **1**: 400, 1946 (DDT).
189. Council on Pharmacy and Chemistry: *J. A. M. A.* **145**: 728, 1951 (pharmacologic and toxicologic effects of DDT).
190. Editorial: *J. A. M. A.* **145**: 735, 1951 (insecticide storage in adipose tissue).
191. Council on Pharmacy and Chemistry: *J. A. M. A.* **147**: 571, 1951 (toxic effects of technical benzene hexachloride and its principal isomers).
192. Kalmbach, E. R.: *Science* **102**: 232, 1945 ("ten-eighty," a war-produced rodenticide).
193. Chenoweth, M. R., and St. John, E. F.: *J. Pharmacol. & Exper. Therap.* **87**: 90, 1946 (pharmacology of fluoroacetate, I); **87**: 90, 1946 (II); **90**: 76, 1947 (III).
194. Richter, C. P.: *J. A. M. A.* **129**: 927, 1945 (alphanaphthylthiourea [ANTU] as a rat poison).
195. Latta, H.: *Bull. Johns Hopkins Hosp.* **80**: 181, 1947 (acute alphanaphthylthiourea in rats and dogs).

Chapter 8

EFFECTS OF RADIATION

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The term radiation has come to include two different forms of energy propagation. One is generally pictured as taking place by means of wave motion and is known as *electromagnetic radiation*, and the other, by the movement of particles such as alpha and beta particles, neutrons, deuterons, and the like, is known as *particulate radiation*. The properties of electromagnetic and particulate radiation are similar in many respects and their biological actions are qualitatively identical.

ELECTROMAGNETIC RADIATION

Electromagnetic radiation forms a continuous spectrum of varying wave lengths ranging from long radio and electric waves at one extreme to very short gamma rays at the other (Fig. 118). According to the classic wave theory all these waves are rhythmic electromagnetic oscillations even though they show some characteristics of particulate radiation. In a vacuum they travel with the speed of light, but when traveling through matter their velocity is slightly less. They may be refracted or reflected, under proper conditions, like ordinary light and differ from one another only in the length of their waves. Electromagnetic waves carry energy which can be given up only in units of determinate size, known as quanta, the quanta of energy being greater with radiation of shorter wave length. Only short wave lengths (roentgen rays, gamma rays) deliver quanta of sufficient energy to produce ionization in tissues, and only exceedingly short gamma rays have enough energy to disrupt atomic nuclei.

Different regions in the electromagnetic spectrum were independently discovered and described over the years and many were given special names before it was recognized that all these wave bands belonged in a single continuous spectrum. It is useful to be familiar with the following terms, which designate successive regions of the electromagnetic spectrum in order of decreasing wave length: electric waves, long radio waves, short radio waves, ultra short radio waves (micro-waves), long infrared rays, short infrared rays, visible rays, near ultraviolet rays, far ultraviolet rays, grenz rays, soft (long) roentgen rays, medium roentgen rays, hard (supervoltage or short) roentgen rays, soft gamma rays, hard gamma rays, and

secondary cosmic rays. The bands that have been given names often overlap and the names do not identify the waves so precisely as a simple statement of wave length. However, the names do have some usefulness since certain properties such as thermal effects, visibility, ability to excite fluorescence or ionization, penetrating power, and absorption often show rapid quantitative changes near the boundaries of adjacent bands.

PARTICULATE RADIATION

Particulate radiation may be generated directly or indirectly by accelerating deuterons, electrons, and the like to high speeds in devices such as the cyclotron and betatron. Cosmic rays are high energy atomic nuclei which reach the earth's atmosphere from outer space. Before their energy reaches the earth most of it is transformed, by absorption in the atmosphere, into short gamma rays known as secondary cosmic rays. Particulate radiation is also generated during the spontaneous decay of a variety of natural and artificial radioactive substances and is given off in enormous quantities during chain reactions in the atomic reactor or pile.

RADIOACTIVE SUBSTANCES

Natural Radioactive Substances

Certain naturally occurring substances such as radium, thorium, actinium, and their decay products give off radiant energy spontaneously. A certain part of this energy may be in the form of true electromagnetic waves (γ rays) but the major portion appears as alpha (α) and beta (β) particles. Alpha particles are helium nuclei in rapid motion and beta particles are negatively charged electrons also in rapid motion. These particles travel at speeds less than the speed of light and like other moving bodies possess energy proportional to their mass and the square of their velocity.

Both natural and artificially produced radioactive substances give off radiant energy as a result of spontaneous disintegration or "decay" of individual atoms. The rate of disintegration is a function of nuclear constitution and cannot be altered by any known physical or chemical means. It is impossible to predict which particular atom will be the next to decay, but in a large aggregation of atoms the statistical rate of disintegration is constant and the rate of production of radiant energy can be predicted.

Each radioactive element or isotope has its own rate of decay which is generally expressed in terms of its "half-life" or the time necessary for one-half the original number of unstable atoms to disintegrate. Each radioactive substance gives off its own specific type of radiation (α , β , γ , or combinations of these) each at a specific energy level. Thus the amount of energy released in the decay of a single atom may differ greatly from one radioactive substance to another.

Alpha particles have little ability to penetrate tissues and thus they give up their large energies within a very short distance. Most beta radiation is more penetrating and the particles may have an average "path" or penetration in tissues of a few millimeters up to a centimeter or more before they are absorbed. When radium is used in the treatment of cancer, it is customary to place it in a metal applicator with walls thick enough to absorb the α and β radiation, allowing only the much more penetrating γ rays to reach the tissues. Therefore the α and β radiations from radium have little practical use in medicine and are important chiefly as a hazard to those who prepare radium needles and applicators.

Artificial Radioactive Substances ("Radioisotopes")

The enormous energies available from very high voltage roentgen-ray machines, cyclotrons, and atomic reactors may be used to disrupt the nuclei of atoms to yield unstable isotopes which then undergo spontaneous radioactive decay. Radioactive isotopes of most of the known elements have already been produced. Their half-lives range from a fraction of a second to centuries and while most of them produce only β radiation, some give off α particles and γ rays. Most of what has been said about radium is applicable to radioactive isotopes and need not be repeated. The special properties of certain isotopes lend themselves to a variety of important medical applications.

Isotopes as "Tracers."—A radioactive isotope of an element is chemically identical with the nonradioactive form and can thus be substituted for it in any chemical compound or reaction. The presence of the radioactive atoms can be detected quantitatively, regardless of molecular combination, by measuring the radioactivity with instruments such as the Geiger counter. Thus it is possible to trace the course of molecules and radicals "tagged" with radioactive atoms through complicated chemical and metabolic processes. This versatile "tracer technique" has almost unlimited potentialities in biochemical and physiologic research and has already provided valuable information on the metabolism of compounds of sodium, phosphorus, carbon, nitrogen, sulfur, iodine, and other elements. Radioactive atoms can be introduced as tracers into many simple and complex molecules by standard chemical methods. Certain biological compounds which are difficult or impossible to "tag" in this fashion can be obtained by supplying plants, bacteria, or animals with radioactive nutrients. After a suitable period of biologic synthesis the

desired radioactive compounds are isolated either directly from tissues or from metabolites. These biologic syntheses have furnished investigators with radioactive vitamins, hormones, alkaloids, antibodies, proteins, and the like and have also shed much light on the synthetic pathways, intermediate metabolism, and degradation of many biologically important substances. In tracer studies the concentration of radioactive atoms is kept so low that the radiation is not likely to disturb normal biologic processes. In most experiments only one unstable atom is employed for each 10^{11} to 10^{15} stable atoms of the same element.

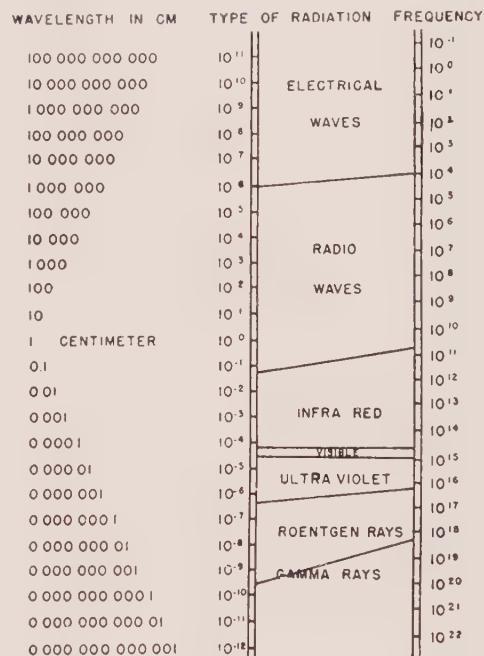


Fig. 118.—The electromagnetic spectrum. Showing wave length and frequency and the names by which different bands of the spectrum are known. The slope of the lines dividing different bands indicates the area of overlapping within which either of two names may be applied to the rays. Wave lengths in angstroms (A) may be computed by multiplying the wave length in centimeters by 100,000,000 (1 cm. = 100,000,000 A). (From Glasser, O.: "Radiation Spectrum," in Glasser, O. [ed.]: Medical Physics. Chicago, 1944, Year Book Publishers, Inc., p. 1164.)

Isotopes in Therapy.—The treatment of human disease with radioactive isotopes is still in the experimental stage. Large doses of isotopes administered to patients will liberate biologically effective quantities of radiation in the tissues. Internal radiation has been used, thus far, mainly in attempts to destroy or damage malignant tumors by taking advantage of the selective concentration of certain chemical elements and compounds in particular organs or tissues. Thus, radioactive iodine like ordinary iodine is concentrated in the thyroid gland and has been used in the treatment of thyroid hyperplasias and cancers. Phosphorus is concentrated in the bones and is also taken up in

the nucleoprotein of rapidly growing cells. In patients with polycythemia and leukemia, radioactive phosphorus concentrates in or near the sites of blood cell formation and interferes with the excessive production of cells. In addition to simple inorganic salts, radioactive organic compounds are being studied in an effort to find substances which will accumulate with sufficient selectivity in specific tissues or lesions to deliver effective local doses of radiation. Direct local injection of isotopes into the tissues may achieve a similar effect. Colloidal preparations of radioactive gold, for example, are chemically inert and remain fairly well localized when injected into and around malignant neoplasms. Since the radioactive decay of gold is rapid, the bulk of the radiation is delivered promptly and the gold need not be removed from the tissues. Preliminary trials of this form of treatment in inoperable carcinoma of the prostate have given some promise of palliative benefit. Radioactive isotopes of long half-life may be enclosed in containers or needles and used like radium either for insertion into the tissues or as external sources of radiation. Radioactive cobalt is already replacing radium in many medical uses since it emits similar high energy gamma radiation and is cheaper, available in larger quantity, and does not, like radium, emit a dangerous radioactive gas in its decay.

Isotopes in Diagnosis.—Little use has yet been made of radioactive isotopes in diagnosis. A number of possibilities are being explored most of which depend on the selective concentration of tracer doses of radioactive compounds in diseased tissues. Thus the presence and location of metastases from carcinoma of the thyroid can sometimes be demonstrated by administering radioactive iodine and then searching the body surfaces with a radiation detector. Any tumor tissue capable of fixing iodine will reveal itself as a local increase in radioactivity.

A great variety of diagnostic applications can be imagined but few have been developed and tested. For example, it should be possible to relate a number of nutritional, metabolic, and endocrine disorders to characteristic abnormalities in the quantity and nature of radioactive excretion products following administration of specific tagged compounds.

INFRARED RAYS

The radiant heat given off by stoves and other nonluminous radiators is in the form of electromagnetic waves in the infrared region of the spectrum. These same "heat" rays are an important component of solar radiation and may be produced artificially for medical uses by infrared or heat lamps.

The only important physiologic effect of infrared radiation is the production of heat within the tissues. The principal action is on the skin and subcutaneous tissues since the rays are absorbed in the superficial 1 to 20 millimeters of tissue, the shorter wavelengths being the more penetrating. The increased tissue temperature increases local circulation by capillary dilatation, accelerates metabolic processes, and

often has a mild analgesic effect. The capillary dilatation increases the vascular filtration surface and favors the formation of edema unless an increased lymphatic flow is able to carry off the excess tissue fluid.

The heating of tissues by infrared radiation is almost immediate without a significant latent period. Erythema or reddening of the skin is apparent within a few minutes after beginning exposure and persists for ten minutes to an hour depending on the duration and intensity of exposure. Excessive exposures produce the edema, blistering, or necrosis of skin characteristic of thermal burns.

SHORT-WAVE DIATHERMY

Electromagnetic waves of longer wave length than the infrared are known as micro-waves or short radio waves (1 to 30 meters). Short-wave diathermy machines generate electromagnetic radiation within this range of frequency and it is well known that by acting as radio transmitters they may interfere with local radio and television reception. However, the term short-wave diathermy is somewhat misleading since it suggests that the patient is treated by electromagnetic radiation. Actually the patient is made a part of a high frequency electric circuit and the tissues are heated by an induced, high-frequency electric current rather than by direct absorption of electromagnetic rays. Short-wave diathermy when properly employed produces a fairly uniform liberation of heat throughout the entire thickness of the treated part and is thus much more effective than infrared exposures in warming deep-seated structures.

ULTRAVIOLET RAYS AND SUNLIGHT

The ultraviolet rays which lie just beyond the violet end of the visible spectrum are an important component of the solar spectrum and are responsible for many of the biologic effects of sunlight. These rays have little penetrating power and are almost completely absorbed in the most superficial layers of the skin. They do not carry sufficient energy to produce ionization in tissues but do cause an activation of the molecules that absorb their energy. The activated molecule may dissipate its excess energy as heat or fluorescence but it may utilize the energy in various photochemical reactions. These are believed to be responsible for most of the biologic actions of visible and ultraviolet radiation. Among the familiar photochemical processes are photography, photosynthesis in green plants, the formation of vitamin D from precursors in irradiated skin, and the killing of bacteria and viruses by light. Among the less desirable photochemical reactions is ordinary sunburn.

Sunburn is a complex response, yet the effects of the different wave lengths in the solar spectrum can be separated to some extent. The infrared rays are responsible for the immediate sensation of heat and the prompt but transient reddening of the skin. The visible portion of the spectrum contributes very little and the

ultraviolet rays are accountable for the major features of the subsequent reaction. Since ultraviolet injury has a latent period of some two to twelve hours, the fiery erythema of true sunburn usually appears after the sun has set. It then persists for hours or days, gradually yielding to a "sun tan" or melanin pigmentation of the skin. In severe sunburn systemic symptoms including fever, headache, nausea, and prostration may appear.

The exact mechanism of injury is obscure but probably involves an initial photochemical change in protoplasmic proteins and nucleic acids. Dead or injured epithelial cells may be found two to three days after exposure in the prickle-cell layer and sometimes in the basal layer of heavily sunburned skin. The severity of systemic reactions shows a striking dependence on the total area as well as the severity of the sunburn and may be caused by absorption into circulation of histamine-like substances or of toxic degradation products of the degenerating epithelial cells.

Repeated exposures to sunlight increase the tolerance of the skin to subsequent exposures and at the same time bring about a progressive pigmentation or tanning of the skin. An associated change, which is not so noticeable, is a progressive thickening of the stratum corneum. Acquired tolerance to sunlight depends chiefly on the protective absorption of ultraviolet light by this thickened surface layer of dead cells and has much less to do with the amount of pigment deposited in the epidermis and dermis.

Considerable individual variation exists in the sensitivity of the skin to ultraviolet light and this limits the usefulness of the "erythema dose" as a clinical unit of exposure. The same person may show variations in sensitivity at different times without relation to previous exposure, and, in women, cycles of sensitivity may coincide with the menstrual cycles.

Persons who show violent skin reactions on moderate exposure to light are said to have abnormal photosensitivity. A variety of fluorescent dyes are capable of photosensitizing biologic systems by serving as light absorbers for certain photochemical reactions. The latter process is known as photodynamic action. It is probable that many persons who suffer from spontaneous or idiopathic photosensitivity have abnormal photosensitizing substances in their skins. In one rare disorder known as porphyria, photosensitivity is attributed to the photodynamic action of porphyrins in the tissues. Porphyrins however, will not explain many cases of light sensitivity.

Prolonged exposure to sunlight over the course of years or repeated exposure to artificial ultraviolet light both appear to accelerate the progress of the senile degenerative changes in the epidermis and dermis that often develop in the aged. Skin showing such premature senile changes is designated as "farmer's skin" or "sailor's skin" and is generally limited to areas not covered by clothing. Hyperkeratoses and carcinomas develop in this skin with such disturbing frequency that one might question the long-term hygienic virtues of both the holiday sun tan and the synthetic ultraviolet lamp variety.

IONIZING RADIATION

Units and Doses

Ionizing radiation includes that portion of the electromagnetic spectrum (roentgen and γ rays) in which the rays carry enough energy to produce ionization in materials which absorb them. It also includes particulate radiation capable of producing similar ionization effects (α and β particles, neutrons, deuterons, protons).

The roentgen (r) has been universally adopted as the unit of dosage for roentgen rays and is also used as a unit for gamma rays. The formal definition is complicated, but in essence one roentgen is the amount of roentgen or gamma radiation which will produce sufficient ionization in a cubic centimeter of air so that the ions will carry one electrostatic unit of electric charge of either sign. In order to represent doses of radiation from β ray and other radioactive sources in terms that will bear some relation to doses of roentgen and gamma rays, a unit has been devised known as the *roentgen equivalent physical or rep.* One rep is 83 ergs of radiant energy absorbed, this being a fair approximation of the energy absorbed by tissues on exposure to one roentgen. The roentgen is a unit of quantity not of rate and in order to represent the intensity of radiation it is customary to speak of *roentgens per hour or per minute.*

Since the roentgen is measured in terms of ionization and since practically all the biologic effects of radiation are thought to be caused by ionization, one might expect that equal doses stated in roentgens would have equal effects on tissues. This is true within limits, but only when other important variables remain constant, such as the wave length of the rays, the distance from the source of radiation to the subject, the intensity (r per minute), the size of the field, and the nature and condition of the tissue.

There is no adequate unit of biologic dosage, but the term "*skin erythema dose*" (S.E.D.) is often used to indicate an exposure just sufficient to produce a definite reddening of the skin. Under ordinary conditions a human erythema dose for a single exposure to roentgen rays generated at 90,000 volts is about 300 r, at 200,000 volts about 600 r, and at 1,000,000 volts about 1,000 r.

The measurement of doses of radiation from radium and other radioactive substances is complicated by the fact that these substances decay at different rates and emit various α , β , and γ radiations at different energy levels. The unit of radium dosage is the *gram-hour* or its subdivisions the *milligram-hour* ($1 \text{ mg.-hr} = 10^{-3} \text{ Gm.-hr.}$) and *microgram-hour* ($1 \mu\text{g.-hr.} = 10^{-6} \text{ Gm.-hr.}$). One gram-hour is the amount of radiation emitted in one hour by one gram of radium element in equilibrium with its decay products. Doses of radium emanation (radon) are measured in *curie-hours*, *millicurie-hours*, and *microcurie-hours*, one curie being originally defined as the amount of radon in equilibrium with one gram of radium element. A milligram-hour of radium and a millicurie-hour of radon have equivalent biologic effects as used in medicine since the α and β radiations are absorbed by

the walls of the standard applicators and the effective γ rays come chiefly from radium C, a decay product in equilibrium both with radium and radon.

Since the curie was originally based on a weighed standard of radium, it proved satisfactory for measuring radon. Difficulties arose when the curie was adopted as a general unit for all radioactive substances and redefined as the number of atomic disintegrations taking place per second in 1 gram of pure radium element. This number, which can be determined only within the limits of experimental error, has been arbitrarily set at the convenient figure of 3.7×10^{10} atomic disintegrations per second and as such is in general use among producers and users of radioactive isotopes. When properly understood this unit is satisfactory even though the amount of energy released per curie may differ by many thousand-fold from one isotope to another.

A new unit, the *rutherford* (rd) has been proposed to replace the curie as a general unit of radioactivity. One rutherford is defined as 10^6 atomic disintegrations per second and one *micro-rutherford* (μ rd) would thus be one disintegration per second. It seems likely that this unit will be adopted since it is an easy number to remember, it fixes an absolute rather than a relative standard of radioactivity, and it avoids the confusion that has resulted from the redefinition of the curie.

It is important to remember that neither the curie nor the rutherford is a measurement of energy. The biologic action of a sample of radioactive material depends on the character and energy of the radiation emitted at each atomic disintegration as well as on the number of disintegrations per second, and if the substance is deposited in the body, the half-life is of great importance. For example, as little as 2 micrograms of radium deposited in the human body is dangerous to life. Radium has a half-life of 1,638 years and together with its poorly soluble decay products subjects the tissues to an unremitting bombardment of energetic α , β , and γ radiations throughout the victim's subsequent life. On the other hand, radioactive phosphorus (P^{32}) has a half-life of 14.3 days, emits only β radiation, and yields no radioactive decay products. Radioactive phosphorus may be given to patients in doses of over 2,000 microcuries and the same dose may be repeated within a few weeks.

Biologic Effects (General Principles)

In discussions of the biologic effects of radiant energy the terms "radiation" and "irradiation" are often loosely used in their several different and overlapping meanings. It is best to use the term "radiation" in referring to the radiant energy itself and "irradiation" to indicate the application of rays to an object. Before describing the changes produced by ionizing radiation in specific tissues and organs, a few of the general principles governing the biologic effects should be stated. These principles are not strict laws but are merely statements of the average experience of clinical and experimental radiologists. It should be re-

membered that radiation has no power to produce effects of a novel kind. As Packard¹⁵ points out, the degenerative and atrophic changes seen in irradiated tissues are not new to pathologists. Heat, cold, electric currents, drugs such as nitrogen mustards, colchicine and podophyllin, and a variety of protoplasmic poisons may produce very similar changes. Neither is the differential sensitivity of various cell types or the enhanced sensitivity of cells in mitosis peculiar to radiation injury. In general, the same cells are damaged selectively by nitrogen mustards, protein breakdown products, arsenic, and a number of other agents. Radiation injuries have no pathognomonic features which distinguish them absolutely from all other injuries, but with experience one can recognize a pattern of changes which is fairly distinctive.

Wave Length, Penetrating Power, Scattering, and Depth Dose.—Roentgen rays and gamma rays cover a broad spectrum of wave lengths, and within this range the shorter the wave lengths the greater the energy and penetrating power of the rays. In ordinary diagnostic roentgenology long wave lengths generated at 30 to 80 kilovolts are used since these give the most favorable selective absorption in tissues of varying composition and density. Although the bulk of such radiation is absorbed in the superficial layers of tissue, enough passes through to give a satisfactory roentgenograph or fluoroscopic image. In radiation therapy shorter wave lengths generated at 100 to 400 kilovolts or more are used in order to deliver a substantial proportion of the energy to deeper structures. Hence machines designed for diagnostic work can seldom be used in roentgen therapy and then only for the most superficial lesions. It also follows that a given dose of radiation from a diagnostic machine will produce greater skin damage and less deep tissue damage than the same dose delivered by a therapy machine.

Gamma radiation, as generally understood, includes a range of wave lengths shorter and more penetrating than ordinary roentgen rays. It may therefore seem incongruous that the gamma radiation from radium is used chiefly to treat local or superficial lesions rather than lesions deep in the body. The explanation involves a simple geometrical principle. Radium is generally employed in "needles" which are embedded in the tissues, or else in applicators applied close to body surfaces. Since the radiation is emitted in all directions, its intensity rapidly decreases as the square of the distance from the source. Thus a cell situated several centimeters from a radium needle receives only a small fraction of the dose delivered to a cell in contact with the needle, and the major effects are limited to the small volume of tissue adjacent to the needle. In roentgen therapy the source of radiation is the target of the roentgen tube which is usually placed from 30 to 60 centimeters away from the patient's skin. This distance is known as the "skin-target distance." Lead shields are used to exclude all but a narrow beam of rays and these rays are not widely divergent but are traveling in almost parallel lines as they enter

the patient's body. If radium were generally available in large enough quantities to be used at comparable distances, its energy could be delivered in a similar narrow beam to deeply seated structures.

The penetrating power of radiation is an important factor in planning the treatment of any lesion. Therapy machines operating at 200 kilovolts will deliver only about 30 per cent of the dose as measured at the skin surface to tissues lying 10 centimeters below the skin, and at lower voltages a much smaller proportion will reach this depth. When radiation is absorbed by tissues, some of its energy is scattered as secondary electrons and as new waves of longer average wave length traveling in various directions through the tissues. The scattered radiation adds its effect to that of the original beam. The larger the volume of tissue exposed, the more scattered radiation there will be and the more important this factor becomes in computing the tissue dose. Since the skin is exposed to larger doses of radiation than reach the underlying tissues, there is danger of producing serious skin damage in attempting to deliver large depth-doses, particularly if large areas of skin are exposed. In order to spare the skin it is often wise to deliver the radiation in successive exposures through several different areas (portals) on the body surface, directing the angle each time so that all beams will converge in the region of the deeply seated tumor. This method of treatment is known as "cross-firing" and permits delivery of a larger cumulative dose of radiation to the tumor than to any one of the several skin portals.

Time-Intensity Factor.—It has been found that a given dose of radiation will produce greater tissue damage if it is delivered in a brief period of time than if the same dose is delivered continuously over a longer span of time or in episodes with intervening rest periods. This may be explained by assuming that a certain amount of tissue recovery occurs and that recovery from previous irradiation may take place even during exposure to further irradiation. It is often desirable to treat malignant tumors by "fractional irradiation," giving a series of moderate doses separated by rest periods of a day or more. In this way a larger total dose of radiation can be delivered and apparently some advantage can be obtained in differential injury to tumor cells as compared to the neighboring normal cells. The exact period of exposure, intensity (roentgens per minute), fractionation, and dose of radiation best suited to the treatment of different types of tumors is not rigidly established, and reputable radiologists often use quite different techniques with equal success.

Latent Period.—One of the most puzzling features of radiation reactions is the so-called "latent period" or time interval between exposure and the first objective evidence of injury. The latent period is shorter with longer wave lengths of radiation and with larger doses. Tissues show a fairly prompt response to injurious doses of infrared rays, but reactions to ultraviolet rays show a distinct latent period of two to twelve hours. During exposure to roentgen rays or radium, even in doses sufficient

to kill tissues, the patient feels no warmth, pain, or any other warning sensation. Some six to forty-eight hours later there may be an evanescent blush known as the early erythema, so slight and so fleeting that it is usually overlooked. The real reaction with sustained erythema and overt skin damage appears from six to fourteen days later, after an interval during which the skin is, to all outward appearances, perfectly normal. Injury is inflicted only during the actual period of exposure and there is no residual or induced radioactivity remaining in tissues after ordinary therapeutic irradiation. Throughout the latent period the injury lurks in the tissue in some obscure form of chemical, cytogenetic or enzymatic change which thus far has eluded explanation. What we recognize clinically as radiation reactions are actually late phenomena in a long and unexplained chain of events.

Mechanism of Action of Ionizing Radiation

Roentgen and gamma rays, together with α and β particles, neutrons, deuterons, and protons, are known as ionizing radiations since they have in common the ability to produce ionization in materials which absorb them. This ionization differs from the spontaneous ionization of salts in solution in that any element or compound may be ionized by radiation. The ionization may be visualized as a momentary loss of an electron from an atom to form an ion pair, followed by prompt reversal of the process and return to a stable state. The state of ionization is estimated to persist for only 10⁻⁸ seconds. Ionizing radiation appears to produce its biologic effects almost entirely through the mechanism of ionization. By this fortunate circumstance almost all the energy released in the absorption of roentgen rays, γ rays, neutron beams, and α and β particles is reduced to a common biologically effective form and the resulting tissue changes are qualitatively similar if not identical. The total energy absorbed in tissues even from a large therapeutic dose of radiation is small, being scarcely sufficient, if transformed into heat, to cause a rise in local tissue temperature of one hundredth of a degree centigrade. The devastating effects are explained by the fact that the energy is not absorbed diffusely and evenly throughout the tissue but in punctate fashion like myriads of tiny bullets. Thus high energies may be delivered to small volumes within the tissues and presumably cause localized injuries within single cells. The distribution of these focal intracellular injuries is accidental and may cause either cell death or mild reversible changes. The concept of localized injuries within a single cell may be somewhat difficult to grasp unless one remembers that a cell is made up of some hundred billion molecules and that a single ionization may affect a single molecule or atom while leaving neighboring molecules unchanged. A further aid in appreciating the discontinuity of effect is supplied by Crowther's estimate that if a volume of air were exposed to roentgen rays at an intensity of 1 r per second, continuously,

day and night for 500 years, one-third of the molecules would still be unirradiated.

In spite of general agreement that biologic effects are causally related to ionization, there is no clear explanation of the precise mechanism of cell injury. One hypothesis proposes that there are within cells vital structures of limited volume, and if one or several ion pairs are formed within this "sensitive volume" the cell will be severely damaged or killed. This concept is variously known as the "target," "quantum hit," or "point heat" theory and has received strong support in experiments in which cell death is used as the criterion of injury. An alternative theory assumes that changes of a more diffuse nature occur within the cell, releasing injurious substances usually assumed to be protein breakdown products or peroxides. Cells succumb or survive according to their individual ability to withstand the injurious substances. This theory does not fit all the known facts, but in some ways it is better adapted to explain the broad range of graded injuries suffered by different cells, the gross similarity of the changes produced by radiation and by protoplasmic poisons, the partial or complete recovery of many cells after initial damage, and also the intracellular postirradiation edema which could result from the breakdown of many large molecules into more numerous osmotically active moieties.

The well-established effects of radiation on cellular genetics furnish still another mechanism of biologic action believed by many to be the most important of all. Irradiated cells show a wide variety of bizarre chromosomal and genic abnormalities in subsequent divisions. Some cells are rendered incapable of mitotic division but continue to build protoplasm and become giant cells. The delayed manifestation of other cytogenetic changes may furnish a clue to the long period of progressive tissue damage which follows a brief single exposure to radiation.

Many other mechanisms have been proposed to explain the biologic action of radiation. Among those that deserve consideration are: (1) inactivation of enzyme systems; (2) coagulation or flocculation of protoplasmic colloids; and (3) denaturation of nucleoproteins.

The inadequacy of all these theories is nicely illustrated by the profound influence of environment on radiosensitivity. For example, none of the theories would lead one to expect a major difference in the radiosensitivity of cells growing in the living body and growing in tissue culture. Yet experiment reveals a five- to one hundredfold increase in the radioresistance of cells when they are irradiated *in vitro* or even when they are irradiated *in vivo* and promptly transplanted to an unirradiated host or explanted to tissue culture.

Radiosensitivity.—While it is possible to kill any living thing with sufficiently large doses of radiation, the median lethal dose for different cells and organisms varies widely. Bacteria, viruses, and some cold-blooded creatures may survive doses in excess of 100,000 r, while Drosophila eggs have a median lethal dose of less than 200 r. Human lymphocytes are damaged by 100 r, but human nervous tissue can withstand 5,000 r. Even cells of identical type and similar appearance are not equally affected by the same dose. Although 100 r will produce degenerative changes in many of the lymphocytes in a lymph node, many times this dose can be given without destroying every lymphocyte in the node.

In view of the wide range of radiosensitivity among cells of a single type, it may seem pointless to claim that one type of cell is more or less radiosensitive than another. However, there are differences in average vulnerability sufficiently large to be of great practical importance. Any classification of cells and tissues in order of their radiosensitivity is inexact since it disregards many other important variables. While the principle of specific tissue sensitivity is sound, no two classifications agree completely. The exact position of any cell or tissue is arbitrary and the following listing should not be taken too literally. Warren has suggested that tumors may be classified as radiosensitive, radioresponsive, and radioresistant when a gross decrease in size follows exposure to doses of 2,500 r, 2,500 to 5,000 r, and over 5,000 r, respectively. Microscopic changes appear at lower doses than gross changes and it would be preferable to use lower ranges of dosage in this classification. However, in order to avoid confusion, Warren's useful categories will be retained.

- I. Radiosensitive (2,500 r, or less, kills or seriously injures many cells).
 - Lymphocytes and lymphoblasts.
 - Bone marrow (myeloblastic and erythroblastic cells).
 - Epithelium of intestine and stomach.
 - Germ cells (ovary and testis).
- II. Radioresponsive (2,500 to 5,000 r kills or seriously injures many cells).
 - Epithelium of skin and skin appendages.
 - Endothelium of blood vessels.
 - Salivary glands.
 - Bone and cartilage (growing).
 - Conjunctiva, cornea and lens of eye.
 - Collagen and elastic tissue (fibroblasts themselves are quite resistant).
- III. Radioresistant (over 5,000 r necessary to kill or injure many cells).
 - Kidney.
 - Liver.
 - Thyroid, pancreas, pituitary, adrenal, and parathyroid glands.
 - Bone and cartilage (mature).

Muscle (all types).

Brain and other nervous tissue (embryonic nervous tissue may be injured by rather small doses).

Cell Differentiation.—In general, embryonic, immature, or poorly differentiated cells are more easily injured than differentiated cells of the same type but once injured may be expected to show greater powers of recovery. This rule applies both to the greater general radiosensitivity of the tissues of young animals and to the special radiosensitivity of undifferentiated cells in adults. The rule is sound as a generalization but is subject to so many particular exceptions that its practical usefulness is limited.

Cell Reproduction.—All cells show an increased vulnerability to radiation injury at the time of mitotic division. The most sensitive stage of mitosis appears to be early prophase or late premitotic phase. Dividing cells arrested in metaphase by the administration of colchicine do not show a significant increase in radiosensitivity over resting cells.

Not only are cells more sensitive to irradiation during mitosis but if they are irradiated during the resting phase they show a delay or inhibition of subsequent mitoses. A sharp decrease in the number of mitotic figures may be apparent within one-half hour after irradiating rapidly growing plant or animal tissues.

Rapidly growing or immature tissues may owe their radiosensitivity in part to the presence of many cells in mitosis, and differentiated tissues may enjoy greater radioresistance partly because mitoses are rare. However, only a small proportion of the cells in a tissue are in mitosis at any one time and the relative abundance of mitoses has been given entirely too much weight in attempts to explain the relative radiosensitivities of different normal tissues and neoplasms. Rapid cell multiplication is characteristic of radiosensitive structures such as the lymph nodes, bone marrow, and gonads, but the liver remains radioresistant even during rapid cellular regeneration, and neoplasms such as malignant melanoma and osteogenic sarcoma may show little response to radiation even though myriads of mitoses are present.

Impairment of Function Without Cell Death.—Death of cells is the most obvious re-

action in heavily irradiated tissue, but cell injury short of death plays an important part in the response to radiation. Sublethal injuries are obvious when they are manifest as changes in cell size, shape, or staining properties, but functional injuries are more difficult to detect and are frequently ignored. A single cell may have a number of functions which are unequally affected by the same dose of radiation. The function of cell reproduction is among the most sensitive, as has already been mentioned, and the basic metabolic functions essential to life are of necessity the last to be destroyed. Differentiated and specialized cells show a variety of functional radiation changes, including a decrease in ameboid motion and phagocytic activity in leukocytes, prompt cessation of ciliary motion in respiratory epithelium, impaired secretion by salivary glands, excess mucus secretion by intestinal mucosa, and decreased acid secretion by gastric mucosa. Important effects on the function of all the endocrine glands have been reported, but the evidence is convincing only for the thyroid and ovary.

Influence of Temperature and Circulation of Blood.—There is considerable scattered evidence that the injurious effects of radiation are decreased if the circulation of the irradiated part is compromised or if the local or systemic temperature is lowered during or after irradiation. Blood flow and tissue temperature are often interdependent, and some investigators have not taken pains to segregate the two factors. Newborn rats exposed to roentgen rays at a body temperature of 4° C. suffer much less skin damage than controls irradiated at room temperature. Similarly, the legs and tails of rats are rendered more radioresistant if the local circulation is temporarily arrested. Sublethal carbon monoxide poisoning or severe systemic anoxia during exposure will also decrease the injurious effects of radiation.

Adequate data on human reactions is lacking, but there is suggestive evidence that either lowered tissue temperature or decreased blood supply will decrease the biologic effectiveness of radiation. It may be that tumors which become refractory to roentgen therapy after repeated exposures do so in part because their blood supply has been impaired by previous irradiation.

Latent Tissue Injury and Cumulative Effects.—Latent tissue injury refers to the residual tissue damage which remains after an initial radiation reaction has subsided. Moderate radiation reactions subside in a few months and the tissues resume a normal gross and microscopic appearance. Although no residual injury can be detected by any ordinary means, this tissue will retain for years an enhanced susceptibility to injury if it is again irradiated. Repeated exposures to very small doses, no one of which is sufficient to evoke a perceptible reaction, can in the aggregate produce serious latent or patent damage. The biologic effects of radiation are cumulative but show incomplete summation. Cumulative injuries are a particular hazard of poorly protected or careless radiological workers.

Tissue Tolerance.—The tissue tolerance dose of radiation cannot be rigidly defined, but the term is used to indicate the maximum dose of radiation which a given tissue can receive without losing its major function, becoming necrotic, breaking down, or ulcerating. Tissue tolerance is the limiting factor in the radiation treatment of cancer, and only those forms of cancer which have a lower tolerance than the normal tissues in which they are growing can be effectively controlled by radiation therapy.

Systemic Effects.—When a portion of the body is irradiated, most of the tissue changes are sharply confined to the volume of tissue within the field of exposure. However, certain generalized or systemic disturbances may also appear. Profound systemic effects can be produced by heavy exposure of any large volume of tissue, even an extremity, but they are most likely to result when the abdomen, and particularly the upper abdomen, is irradiated. The three common forms of systemic disorder are radiation sickness, radiation cachexia, and radiation changes in the blood.

loss of weight, depression, and muscular weakness. It appears insidiously several weeks or months after massive exposures and is often associated with anemia and leukopenia. It is not a self-limited disorder like radiation sickness. In some patients recovery is satisfactory; in others the disorder stabilizes at the level of chronic ill-health, but more often the symptoms become progressively severe and death results in a few months. It is probable that no single factor is responsible for radiation cachexia but that the symptoms reflect a summation of injuries affecting several organ systems.

Radiation changes in the blood will be discussed at greater length in a later section. Leukopenia can be produced quite readily and massive doses can cause severe anemias. The effects are attributable almost entirely to direct and indirect injury of the blood-forming organs rather than to massive destruction of cells already in circulation.

Permissible or "Tolerance" Doses.—Under the best of conditions radiological workers are exposed to minute doses of radiation. Strict at-



Fig. 119.—Roentgen-ray burn of the hand with radiation ulcer. The patient was given improper roentgen treatments of the whole hand repeatedly over a period of three years, for a small lesion suspected of being cancer. When photographed, the hand was practically useless and so painful that it was subsequently amputated. No cancer was found. Note the generalized edema and scaling of the skin and the characteristic chronic radiation ulcer with sharp smooth edges and necrotic base. (Courtesy Dr. Manuel Garcia. From Occup. Med. 1: 1946.)

Radiation sickness is characterized by nausea, vomiting, and acute psychic depression, coming on promptly or within a few hours after exposure and seldom lasting more than forty-eight hours. Its pathogenesis is poorly understood but there is reason to believe that tissue breakdown products reaching the circulating blood play an important part. Uneventful recovery is to be expected, but the symptoms are likely to recur with further irradiation. Similar symptoms, of psychic origin, may develop in suggestible or apprehensive patients, but real radiation sickness is beyond question an organic disorder.

Radiation cachexia is a slowly progressive apathetic state accompanied by poor appetite,

tention to the details of protection will reduce these doses to levels which will not produce detectable injury in normal tissues. A dose of 0.1 r of roentgen or gamma rays per day delivered to the whole body is considered safe by most radiologists although some geneticists fear that repeated exposure even to this small dose is capable of producing cumulative genetic injuries. Since the actual safe dose or "tolerance dose" is not known and would be difficult to determine in human beings, and since "tolerance" is often used in a different sense by radiologists, it is preferable to use the term "permissible dose" rather than "tolerance dose."

The permissible doses of internally administered radioactive substances must be de-

terminated for each substance individually. There is particular danger in elements of long half-life such as radium, polonium, strontium (Sr^{89}), and carbon (C^{14}), all of which may be deposited in bone in substantial quantities and are then not excreted rapidly. Short-life isotopes and those which are excreted rapidly have higher permissible doses and are safer to use in human tracer studies.

Effects on Specific Tissues and Organs

Skin.—Of all tissues the skin is most frequently damaged by radiation, as one might expect from the fact that all external radiation must pass through the skin before reaching deeper structures. During exposure even to high intensities and large doses, no subjective or objective change in the skin can be detected by present methods even though we know from subsequent events that very important changes must be taking place. Some six to forty-eight hours after exposure a faint blush (early erythema) may be seen in the treated area but this is so inconstant and transient that it is seldom noticed.

At the end of the latent period, usually six to fourteen days, a sustained erythema develops. Grossly and microscopically the reaction resembles an ordinary sunburn if one can imagine a sunburn not confined to the superficial layers of the skin but extending deeply into the tissues. The intensity and duration of the reaction is greater with larger doses and, like sunburn or thermal burn, may be classed as first degree if limited to transient erythema, second degree if the epithelium is seriously damaged and blistering or desquamation results, and third degree if there is extensive destruction of both epidermis and dermis. This classification is of limited value in radiation burns since the early surface appearance does not reflect accurately the more important deeper injuries to dermal and subcutaneous collagen and blood vessels. At first the erythema is bright red, but within a few days it takes on a darker red or purplish cast. A variable degree of edema develops at about the same time and in heavily irradiated skin the edema may persist for weeks or months, long after the erythema has subsided. The excess fluid appears to be more firmly bound than in the ordinary forms of acute edema and much of it is incorporated in swollen, degenerated collagen and elastic tissue, while some is within swollen cells. Loss of hair and loss of function of sweat glands and sebaceous glands follow exposure to doses even less than an erythema dose. These changes are reversible or permanent depending on the size of the dose.

Microscopically, little change is visible during the latent period, but just before the erythema is expected endothelial swelling appears and the collagen bundles and elastic tissue fibrils in the dermis and in the walls of blood vessels begin to swell. Longitudinal fibrillation of collagen bundles develops and the fibrils often break transversely at several points and separate from one another. Collagen bundles soon lose their normal, clear, pink appearance when stained with eosin and take a muddy, granular, brick-red stain. Elastic tissue fibrils swell to several times their original diameter and rupture trans-

versely. The broken ends become frayed and the fibrils curl up in irregular arcs and spirals. The damaged, swollen fibrils may take an uneven, dark-purple stain with hematoxylin, giving the false impression that there has been proliferation of much new elastic tissue.

Edema is apparent not only in the swelling of pre-existing structures but as an increase in the size and number of tissue spaces. In the early phases of the reaction the free edema fluid seldom contains enough protein to coagulate on fixation, but later the tissue spaces instead of appearing empty are filled with a pale pink-staining protein coagulum.

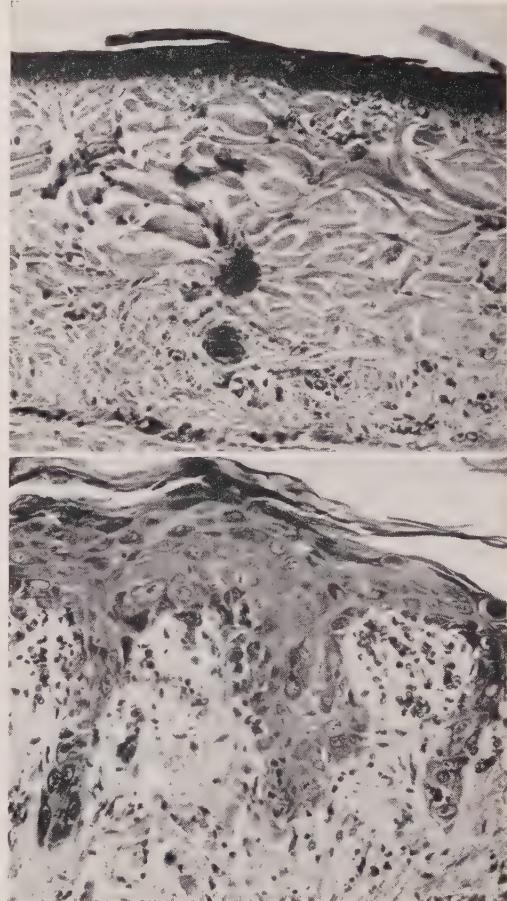


Fig. 120.—Experimental radiation reaction in rabbit skin, six days. Top: Normal, showing thin layer of small epithelial cells and well-preserved bundles of collagen. Bottom: Six days after exposure to 200 mc-hr. of lightly filtered radon. Note the bizarre shapes and tremendous swelling of epithelial cells, loss of the basement membrane with downward projections of epithelium. In the dermis, scattered inflammatory cells are seen and disruption and fibrillation of collagen bundles. (Both at same magnification— $\times 160$.)

Scattered inflammatory cells appear soon after the first evidence of degenerative change and edema, their numbers depending more on the degree of degeneration than on the amount of edema. Neutrophilic polymorphonuclear

leukocytes appear first, but only in small numbers, and are soon replaced by scattered macrophages, eosinophiles, and small dark-staining cells resembling lymphocytes and plasma cells. The cellular infiltrate is sparse and does not show the distinct perivascular localization so common in other forms of dermatitis. Significant amounts of fibrin are present only in severe, acute reactions. Degeneration and swelling of collagen and smooth muscle in the walls of small blood vessels, together with swelling of endothelial cells, may narrow or close the vessel lumina, and thrombi form in occasional vessels. There is a striking lack of uniformity in the vascular changes, seriously damaged vessels and normal vessels often appearing side by side.

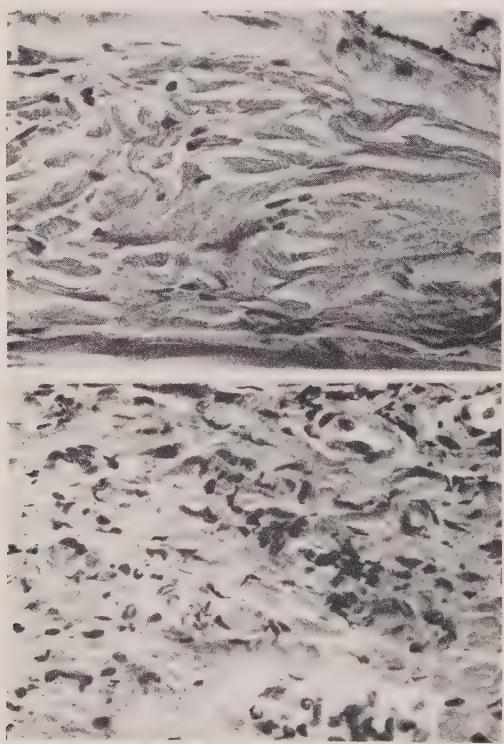


Fig. 121.—Experimental radiation reaction in collagen, twenty days. Rabbit skin. Top: Normal. Bottom: Twenty days after 200 mc.-hr. lightly filtered radon. Note the fragmentation and disorganization of collagen bundles, the atypical fibroblast nuclei and the endothelial swelling. Scattered inflammatory cells are still present. (Both at same magnification— $\times 370$.)

If the dose of radiation has been moderate, the acute reaction is followed by a slow repair of the surface epithelium and skin appendages and a return of the dermal structures toward normal. Within a few months all histologic evidence of radiation injury may have disappeared and no changes will remain to suggest the presence of latent tissue injury. Nevertheless, if the same region is again exposed to

a dose of radiation which normal skin would readily tolerate, a reaction of untoward severity will develop.

When skin is exposed to excessive doses, obvious and permanent gross and microscopic damage results. As the early reaction subsides, a series of slow changes sets in which may progress for months or even years. The acute swelling of the dermis gives way to a chronic phlegmonous or "woody" edema as coarse bundles of collagen are gradually laid down. These slowly hyalinize and may fuse with one another or with pre-existing collagen bundles. A few bizarre, irregularly shaped or giant fibroblasts persist in the resulting scar tissue. The blood vessels do not show a uniform reaction. Some atrophy and disappear, in much the same fashion as blood vessels in granulation tissue disappear with time. Others remain patent but develop hyalinized, rigid, and inelastic walls, and still others dilate to form permanent telangiectases. Little if any new elastic tissue is formed and the skin becomes thickened, woody, inelastic, and almost avascular.

Successful repair of the surface epithelium and skin appendages is intimately dependent on the recovery of the corium and its blood vessels. Within the same field of treatment the corium may show patchy variations in the degree of scarring and where it is best preserved the surface epithelium and skin appendages regenerate most successfully. In regions of dense scarring the rete pegs are flattened out and the epithelial cells of the skin appendages either disappear entirely or persist only as small downward projections and isolated nests of simple squamous epithelium. The surface epithelium is reduced to a few layers of flattened squamous cells and the basement membrane disappears. Such regions heal poorly after surgical or accidental trauma, have poor resistance against bacterial infection, and may break down spontaneously to form chronic or recurrent radiation ulcers. Grossly the skin is tense, shiny, dry, and atrophic, with irregular regions of pigmentation and depigmentation and spiderlike ramifications of telangiectatic vessels. Focal patches of hyperkeratosis often appear and carcinoma may develop in such areas at any time from two to thirty years or more after exposure.

Gastrointestinal Tract.—Although the stomach and intestines are quite radiosensitive, serious injuries are not frequent in ordinary radiologic practice. The body wall affords some protection to the gastrointestinal tract and radiologists are conservative when administering radiation to the abdomen because of the danger of adverse reactions. The duodenum and small intestine appear to be more vulnerable to injury than the stomach. The colon is somewhat more resistant and the rectum in most instances is able to withstand the heavy doses to which it is exposed in the routine radiologic treatment of carcinoma of the cervix.

The earliest radiation changes seen in the gastrointestinal tract are edema, degeneration, and necrosis of mucosal epithelial cells, and submucosal edema. These acute changes appear within a few hours and may be responsible for many of the symptoms of radiation sickness.

Mitotic figures promptly disappear, indicating a temporary failure of normal regenerative activity. The damaged epithelial cells soon develop bizarre distorted forms with swollen and irregular nuclei and some of them slough off into the lumen of the intestine. The proportion of mucous cells increases at the expense of crypt cells and the production of mucus increases. In more severe injuries vascular damage occurs, degeneration of collagen is greater, and edema appears in all layers of the intestinal wall but chiefly in the submucosa and subserosa. Extensive atrophy of the glandular mucosa develops and may persist for months. Regeneration makes its appearance after a variable interval of weeks or months. The mucosa is completely restored in some regions, while in others atypical hyperplastic glands and small cystic glandular inclusions are formed. Normal structures in the bowel wall may be replaced by dense, hyaline material lacking the fibrillar structure of normal collagen. Focal dilatation or ectasia of veins and lymphatic vessels is prominent, while most of the arteries are unaffected. The intestinal lymphoid tissue disappears early in the reaction and seldom regenerates completely.

to the mucosa and submucosa or may penetrate deeply into or through the muscularis. In general, the borders of ulcers are well defined and their walls steep. A nonspecific inflammatory reaction of varying intensity surrounds the ulcer. Like radiation ulcers of the skin, the base and sides of the intestinal ulcers are formed of poorly vascularized connective tissue and the lesions heal poorly. The overlying serosa is often white and grossly thickened and is traversed by telangiectatic veins. The ulcers have no characteristic size, shape, or distribution and may be single, multiple, focal, annular, or segmental. Segmental induration of the bowel wall may be present with or without ulceration of the mucosa. Intestinal perforation and fistula formation are not uncommon.

It is probable that secondary bacterial infection plays an important part in the genesis and localization of radiation injuries of the intestine. Bacterial clumps are common in both the early and the late lesions, and the distribution of ulcers along an irradiated segment of intestine is often fortuitous and does not correspond strictly to the distribution of maximal irradiation. Ulcers of similar appearance may occur at any level from the stomach to the anus, and



Fig. 122.—Chronic radiation ulcer of the skin of the groin. This surgical specimen came from a 75-year-old woman who had received 5,000 r of roentgen radiation to this area eight months previously as treatment of carcinoma of the cervix. The sharply delimited rectangular ulcer corresponds roughly to the original portal of treatment. Note the brawny induration and ischemic appearance of the ulcer margins and the necrotic ulcer base. The specimen demonstrates the result of excessive treatment and also illustrates the proper surgical treatment of radiation ulcers, by wide and deep excision, well beyond the limits of obvious tissue damage.

Superficial mucosal ulcerations may appear within the first few weeks of the reaction, but most of these are small and soon heal. Chronic radiation injuries of the intestine characteristically develop from six months to several years after exposure. They are usually painful and respond poorly to treatment. The most common lesions are chronic ulcers which may be confined

the higher statistical frequency of rectal ulcer is related to the large number of patients who receive combined radium and roentgen therapy for carcinoma of the cervix.

Effects of radiation on the function of the gastrointestinal tract have not been thoroughly studied. Fairly large doses cause a prompt and prolonged depression of acid and pepsin

secretion in the stomach, and this effect has been employed in the management of peptic ulcer. Increased mucus production in the small intestine and colon is frequently reported. Normal intestinal absorption is impaired after irradiation, but the permeability of the intestinal mucosa to ingested foreign proteins appears to be increased. Muscular tone and peristaltic activity are said to be increased.



Fig. 123.—Radiation reaction in muscle. Biopsy of tongue of 80-year-old Negro man, twelve months after heavy roentgen therapy and radium implants for carcinoma of the tongue. Even the radiosistant striated muscle fibers have been destroyed and replaced by coarse bundles of collagen. A diffuse low-grade inflammation is present. A few muscle cell nuclei survive as distorted giant forms. The clear, slitlike spaces are filled with edema fluid and the two larger, rounded spaces are telangiectatic blood vessels.

Bone and Cartilage.—Mature bone is quite resistant to radiation injury, but the endochondral growth of bone in children may be impaired even by moderate exposures. Ordinary diagnostic roentgenography does not subject growing bones to dangerous exposures, and most of the reported injuries have resulted from the use of excessive doses in therapy. An important potential hazard exists in the fluoroscopic installations present in many shoe stores. These devices enable the customer and his children to obtain a fascinating view of the position of the bones of the foot within the new shoe. When the machine is operated according to the directions of the distributor a single exposure is not dangerous, but the opportunities for innocent abuse are obvious.

Profound histologic changes are seen after irradiation in the growing epiphyses of experimental animals and it is probable that similar changes occur in human beings. The orderly parallel columns of epiphyseal cartilage cells become disarranged early in the reaction, the cartilage cells swell and the intercolumnar cartilage matrix takes on a mottled and fibrillar appearance. There is interference with the normal degeneration of the cartilage cells at the diaphyseal end of the columns and capillaries do not invade the cartilage lacunae successfully. Interference with the normal processes of cartilage growth, maturation and dissolution appears to be more important in arresting growth than direct damage to the osteoblasts. In fact, the continued activity of osteoblasts may result in thickened trabeculae of bone in the diaphyseal region when longitudinal growth has been arrested by damage to the cartilage. After minor injuries growth activity may be resumed at a normal rate, but greater damage results in a sustained retardation or arrest of growth.

Mature bone enjoys fairly good radioresistance and is seldom injured except in persons subjected to heavy radiation therapy or in those who have acquired radioactive deposits in their bones. Spontaneous asymptomatic fractures of the ribs sometimes occur in women who have been irradiated for carcinoma of the breast, and spontaneous fractures of the neck of the femur have been reported as occurring several months after radium and roentgen therapy of carcinoma of the cervix.

The bone changes resulting from irradiation have never been thoroughly studied and are generally designated by the unsatisfactory term "radiation osteitis." Actually there is very little inflammation and the changes are similar in many respects to those seen in ordinary sterile necrosis of bone. The chalky brittleness of heavily irradiated bone suggests an alteration in the physical structure of the matrix substance and some fibrillation and disorganization of the matrix can be seen microscopically. Periosteal activity may succeed in depositing a thin layer of poorly formed living bone over the regions of necrosis much as an involucrum forms about a sequestrum in osteomyelitis. Necrosis of bone occurs in irregular, large or small patchy areas, and there is seldom a clear line of demarcation between dead and living bone. Frank sequestration of the necrotic bone is not characteristic unless there is secondary infection. Bones subjected to heavy irradiation are thereafter highly susceptible to bacterial infection. The resulting osteomyelitis is progressive and responds poorly to conservative treatment.

Extensive radiation injury to bone often goes undetected. The lesions are sometimes excruciatingly painful but for the most part they are entirely asymptomatic unless complicated by fracture or infection. Roentgenographs will usually reveal irregular areas of increased or decreased density but these changes may be minimal. There is no satisfactory clinical method of discovering damage to the matrix or even death of the bone unless there is an associated change in the concentration or distribution of calcium salts detectable by roent-

genography. Pathologic fractures in such regions are accompanied by surprisingly little pain but are nevertheless quite troublesome since they heal poorly. A few osteogenic sarcomas and chondrosarcomas have arisen in regions of old radiation osteitis, but this complication is rare as a consequence of external roentgen irradiation.

Internal deposits of radioactive substances may produce bone changes similar to those already described. Substances with a long half-life that are selectively deposited in bone (radium, polonium, radioactive strontium, etc.) will produce radiation osteitis regularly when administered to experimental animals in adequate doses. Until recent years the only major hazard of human poisoning with radioactive materials existed in the luminous dial industry. Luminous paint contains minute quantities of radium, and workers engaged in painting dials by hand were accustomed, before the hazard was recognized, to bringing their brushes to a fine point by drawing the bristles between their moistened lips. Each day they ingested a small quantity of luminous paint. Most of the radium was promptly excreted but a fraction was deposited in bone. Martland's description²⁰ of the relentless progress of bone and bone marrow injuries in a group of these persons should serve as a warning to anyone handling or administering radioactive substances. Many of the victims developed radiation necrosis of the mandible, others died of intractable, progressive anemia and leukopenia, while a considerable number lived long enough to develop osteogenic sarcoma in regions of radiation osteitis. These effects were produced by almost inconceivably small quantities of radium, the total body content ranging from 2 to 180 micrograms. The production of osteogenic sarcoma by radioactive deposits in the bones has been confirmed repeatedly in animal experiments using a variety of radioactive substances.

Lungs.—When the lungs are heavily irradiated as they may be in the treatment of carcinoma of the breast or esophagus, they sometimes but not always show a characteristic reaction known as radiation pneumonitis. Grossly the lungs become dry, rubbery, pale, and subcrepitant, with a suggestion of diffuse fibrosis. The salient histologic features are edema and thickening of alveolar walls, with slight to moderate fibrosis, swelling, and desquamation of alveolar lining cells, a pink-staining "hyaline membrane" closely applied to occasional alveolar walls, hyalinization of arterial walls, and endothelial swelling in alveolar capillaries, all occurring with little associated acute inflammatory exudation. These changes may be irregularly distributed in the lung and need not all be present together. In extreme cases the respiratory function of the lung is sufficiently impaired to cause dyspnea, but more often the principal clinical feature is a hacking nonproductive cough. There may be some associated pain. Early or acute reactions may subside to leave a fairly normal lung but if extensive fibrosis occurs the change is irreversible.

Blood and Blood-Forming Organs.—Routine radiation therapy seldom causes serious or

permanent changes in the circulating blood. However, exposure to large doses of roentgen rays, radium, or other radioactive substances or exposure of large areas of the body to smaller doses often produces severe damage to the blood-forming organs and changes in the circulating blood. In extreme cases death may result from agranulocytosis, anemia, or purpura.

Jacobson and his co-workers²² have made the interesting observation that damage to the blood-forming organs is decreased and recovery of the bone marrow and circulating blood cells is accelerated by protecting the spleen of animals with a lead shield during heavy general body irradiation. There is also evidence that parenteral administration of normal cells from the spleen or bone marrow in an irradiated animal may hasten recovery of the hematopoietic system.

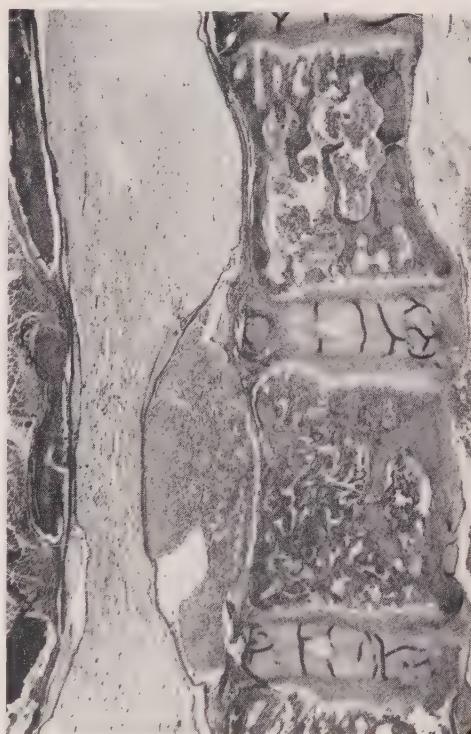


Fig. 124.—Osteogenic sarcoma in radium poisoning. This rat developed paralysis of the hind-quarters 426 days after ingesting radium. The photomicrograph shows a small osteogenic sarcoma arising from a region of radiation osteitis in the second thoracic vertebral body. The neoplasm has protruded into the spinal canal, compressing the spinal cord to less than half its normal diameter. The dura has not been invaded and is seen as a dark line running along the lower border of the neoplasm. ($\times 6$)

Red cells, white cells, and platelets actually in circulation are fairly resistant to radiation injury and changes in the number of circulating elements must be attributed in large part to damage inflicted on the blood-forming organs. There is, however, some increase in the rate of red blood cell destruction as shown by the

prompt appearance of red blood cells in lymph nodes, by deposits of hemosiderin in the lymph nodes, spleen, and bone marrow and by an increased excretion of fecal urobilinogen and urinary bilirubin. If we assume that the average life expectancy of circulating lymphocytes is a few hours, of granulocytes a few days, and of red cells six weeks or more, it follows that simultaneous damage to all hematopoietic tissue would be reflected in the circulating blood, first as a fall in the lymphocytes, then in the granulocytes, and much later in the erythrocytes. Just this sequence of events is seen in heavily irradiated subjects. Within a few hours after exposure the lymphocyte count begins to drop and decreases for about three days. The granulocytes after a brief preliminary rise begin to fall and reach their lowest level in some six days. The red cells, if they are affected at all, seldom show significant change for several weeks. The cells that are most easily damaged show the earliest and most complete recovery. In uncomplicated radiation lymphopenia the lymphocyte count is usually restored to normal within a few weeks; granulopenia often persists for several months, and radiation anemias recover very slowly and often incompletely. After repeated slight injury to blood-forming organs there may be a compensatory hyperplasia with an increase in the circulating lymphocytes, granulocytes, or erythrocytes to levels slightly above normal. Although these reactions are exceptional and usually mild, they may be important as indications of inadequate protection in persons subjected to occupational exposure to radiation. Irradiated mice show an increased incidence of leukemia, and professional radiologists are said to have a tenfold higher incidence of leukemia than physicians not engaged in radiology. A change in the circulating blood cells is the best single indication of inadequate protection in radiological workers. Blood counts should be done on all such workers at regular intervals and any significant lymphocytosis, lymphopenia, leukopenia, or anemia should be considered as presumptive evidence of overexposure.

Work reported to date has failed to establish any constant or dependable change in the water, sodium, chloride, calcium, phosphorus, cholesterol, nitrogen, sugar, or hydrogen-ion concentration of the plasma as a result of therapeutic irradiation in human beings. In many patients there is a transient shortening of coagulation time, together with a brief drop in blood pressure. After heavy exposures, injury to reticuloendothelial tissue may result in impaired ability to produce antibodies, and bacteremia is common. Studies on laboratory animals suggest that the profound hemorrhagic manifestations produced by acute massive exposures result not only from a decrease in platelets but in part from liberation of heparin or a heparin-like substance into the circulating blood. There are no pathognomonic features of radiation changes in the blood, and a history of possible exposure is necessary to support such a diagnosis.

Morphologic changes in the lymph nodes can be detected within an hour after heavy irradiation. In addition to a prompt decrease in the number of mitotic figures, scattered

lymphocytes show pyknosis and fragmentation of nuclei. These changes are progressive with time, and two or three weeks later the lymph node may be reduced to a loose reticulum of fibrous tissue containing deposits of hemosiderin and only a few scattered lymphocytes, reticulum cells, and plasma cells. The endothelium of blood vessels shows swelling and degeneration of cells very similar to that seen in any irradiated organ, but the destruction of lymphocytes appears to be a direct effect of radiation rather than a consequence of impaired circulation. Although the original stroma of the lymph node appears more prominent because of the loss of lymphocytes, there is actually very little formation of new fibrous tissue. Regeneration often begins while destructive changes are still going on. Regeneration may be perfect after minor injury but serious damage is never completely repaired. Many physicians believe that irradiation of lymph nodes will "close off" lymphatics and delay metastases of malignant tumors, but in the few experimental investigations on this point there has been no evidence that the flow of lymph through a lymph node is impaired after irradiation.

The bone marrow shows evidence of radiation damage a little later than the lymph nodes, but the changes are similar. At first, scattered cells degenerate, but within a few days almost all the hematopoietic tissue in a heavily irradiated region is wiped out. There is little evidence of differential radiosensitivity between the myeloblastic and erythroblastic cells in the early reaction. The contents of the marrow space may be reduced at first to a very loose reticulum containing degenerating cells, dilated blood sinusoids, and sometimes frank hemorrhage. Very soon the sinusoids disappear and slight fibrosis occurs, together with attempts at marrow regeneration. Regeneration may fail to appear and the marrow then remains a reticulum of loose fibrous tissue containing hemosiderin deposits, scattered small dark-staining cells, plasma cells, eosinophiles, and an occasional megakaryocyte. Occasionally one finds excessive compensatory regeneration. The marrow is then packed with immature myeloblastic and erythroblastic cells which apparently fail to reach circulation. In either case the peripheral blood shows the leukopenia, thrombocytopenia, and anemia characteristic of aplastic anemia.

Reproductive Organs and Reproduction.—The ovaries and testes are highly sensitive to damage by any form of ionizing radiation, and sterility is easily produced in either sex by a single exposure or by the cumulative effects of repeated small exposures. A single dose of 500 roentgens delivered to the ovaries is sufficient to produce permanent sterility in most women, while somewhat smaller doses result in temporary suppression of ovulation and menstruation. The minimal sterilizing dose is said to be less for men than for women, but few quantitative data are available. Experience with human beings and experimental animals has revealed greater differences in individual susceptibility to sterilization than to most other radiation effects. In general, the young and vigorous withstand much larger doses than older or debilitated subjects, but there is no means of

predicting how a particular person will respond to an exposure near the minimal sterilizing dose. Several times this dose is necessary to assure permanent sterilization of all subjects.

Histologic changes in the irradiated ovary appear within a few hours after exposure. Degeneration of the granulosa cells of maturing follicles is the first evidence of injury, but it is soon followed by degeneration and gradual disappearance of ova from the maturing follicles and most of the primordial follicles. Corpora lutea are little affected even by large doses, but the stromal cells show gradual progressive damage and the weight of the ovary decreases notably. A few primordial follicles with their ova intact will often persist for many months in women who are functionally sterile and it is these surviving follicles that account for the return of ovulation in some women. Temporary sterility as evidenced by suppression of menstruation may last over a year, but if recovery is to take place it generally occurs within the first two to eight months after exposure. The symptoms of radiation sterilization in women resemble those of surgical castration or natural menopause. Since follicle maturation, ovulation, and corpus luteum formation all cease, the menstrual cycle disappears and the endometrium assumes a stable state of hypoplasia. Some women experience hot flashes, psychic depression, and other familiar manifestations of the menopause. No means is known of reversing the injury but hormonal therapy may help to relieve the symptoms.

In the testes the most radiosensitive element is the germinal epithelium. The germ cells in the intermediate stages of spermatogenesis appear to be more easily destroyed than either the spermatogonia or the mature spermatozoa. Thus, a man who has been exposed to a temporarily sterilizing dose may continue to pass living sperm for the next few weeks, but since few if any new spermatozoa are being formed his sperm count gradually falls below the level of fertility. After a variable period of relative or absolute sterility the surviving spermatogonia resume the process of spermatogenesis and the sperm count rises. Recovery is seldom complete but fertility may be restored. During the period of oligospermia the ejaculate contains an increased proportion of dead and abnormal spermatozoa. Larger doses of radiation result in complete and permanent cessation of spermatogenesis and the ejaculate soon becomes devoid of spermatozoa. Even though spermatozoa are more radioresistant than spermatocytes, they may be injured or destroyed by relatively small doses. Frog spermatozoa irradiated *in vitro* may retain motility and ability to fertilize ova while suffering such damage to the nuclear material that the male chromosomes take no further part in development. The resulting embryos are haploid, having only half the normal number of chromosomes, all of them derived from the ova.

The Sertoli cells of the testis survive doses of radiation that destroy the germinal epithelium. The interstitial cells are even more resistant, showing little change in number, appearance, or apparent function even when all the germinal cells and most of the Sertoli cells have

been destroyed. Since the radioresistant interstitial cells are believed to produce most of the male testicular hormones, a man sterilized by radiation does not suffer any serious endocrine disturbance. The testes become smaller and softer, but potency and ejaculation are seldom impaired. There is no obvious change in the victim's social behavior or in his beard, voice, pubic hair, or other secondary sex characteristics. Thus a man may be effectively sterilized without its becoming apparent to himself, his wife, or his friends.

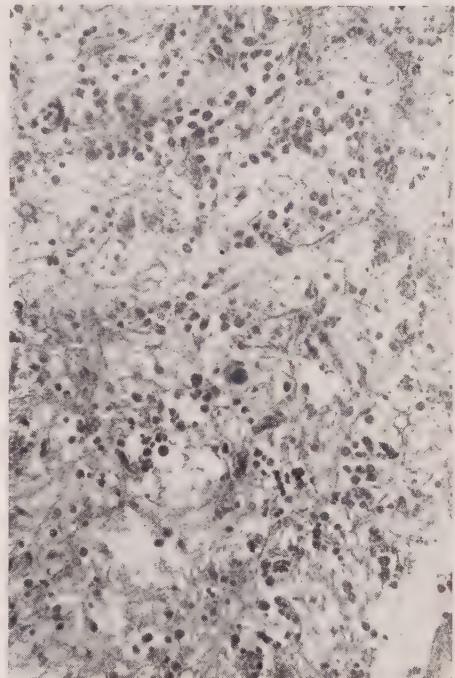


Fig. 125.—Radiation reaction in vertebral bone marrow. Nagasaki atomic bomb victim. The photomicrograph shows a scattering of partially degenerated hematopoietic cells, held in loose, edematous reticulum. Normally, this marrow should be well filled with hematopoietic cells. (Tissue through the courtesy of Dr. Shields Warren.)

The possible effects of substerilizing doses of radiation on the progeny of irradiated parents has received a great deal of attention, particularly since the atomic bombing of Hiroshima and Nagasaki. Two independent problems are involved: first, will irradiation of the gonads of either parent before conception of a child so damage the parent's germ cells that the child or its progeny will be abnormal; and second, will irradiation of the pregnant uterus injure the fetus growing within it? It has long been known that roentgen and gamma irradiation will injure chromosomes and increase the rate of genetic mutations in many plants and insects. Similar chromosome changes have been found in the germ cells of higher forms of life, but no great increase in fetal abnormalities has as yet been demonstrated among the progeny of irra-

diated mammals. This is perhaps not surprising since the great majority of genetic mutations are lethal and most of the others are recessive and may not express themselves as somatic abnormalities for many generations, if ever. Studies of the reproductive history of a considerable number of professional radiologists and radiological technicians have shown a general decrease in fertility but no significant increase in the number of abnormal children.

On the other hand, heavy irradiation of the pregnant human uterus is very likely to result in abortion or defective growth of the fetus, particularly if exposure occurs during the early months of pregnancy. A dose of 1,200 r or more, delivered to the uterus during the first four months of pregnancy, generally results in death of the fetus and abortion. The effects of smaller doses or exposure in the later months of pregnancy are not predictable. The fetus may die or may develop normally, but about 20 per cent of the babies born after having been irradiated in utero are reported to suffer major malformations such as microcephaly and developmental defects of the eyes, limbs, and central nervous system. The amount of radiation received by the fetus during diagnostic radiography of the mother's pelvis during pregnancy is not considered dangerous, but since the tolerance dose of the fetus is not known, unnecessary or repeated diagnostic exposures should be avoided.

RADIATION TREATMENT OF NEOPLASMS

Curative Treatment.—Radiation finds its greatest therapeutic usefulness in the treatment of malignant neoplasms but only tumors of certain types, sizes, and locations lend themselves to successful radiotherapy. It is theoretically possible to destroy any tumor with sufficient irradiation but the objective in this form of treatment is to spare the normal tissues in which the tumor is growing. Thus curative treatment is limited to neoplasms which can be killed by doses of radiation which will permit survival of the surrounding normal tissues. It is also essential that the tumor be confined to a small enough volume of tissue to permit the use of full dosage, that the tumor be in an accessible region of the body, and that it be so situated that large doses can be administered without danger of untoward effects on important neighboring organs. Even when all these conditions are satisfied, radiation therapy is not used if another form of treatment can be expected to yield superior results. In this connection it is well to remember that the efficacy of treatment in radiology, just as in surgery, depends as

much on the skill and experience of the operator as on the adequacy of his tools.

Surgery remains the treatment of choice in the majority of malignant neoplasms but radiation has definite advantages in the primary management of certain specific tumors including carcinoma of the cervix and vagina and some carcinomas of the skin, lip, tongue, oral cavity, pharynx, and larynx. Surgery is preferable to radiation in the management of carcinoma of the breast and most adenocarcinomas, possibly excepting those of the endocervix and endometrium. Sarcomas, in general, respond poorly to irradiation as do malignant melanomas, meningiomas, and carcinomas of the lung, stomach, colon, kidney, pancreas, and liver.

Proper radiation treatment of neoplasms requires the administration, within a brief period of time, of a dose which approaches the tolerance of the normal tissues. The full treatment must be delivered within the span of a few weeks in order to obtain maximum benefit. Thus the radiologist cannot wait to observe the severity of the reaction to each exposure but must plan his entire series of treatments in advance and must be able to predict the total effect. When physicians who lack adequate training attempt radiation therapy, tragic failures to cure initially curable tumors and disfiguring radiation burns are the usual results.

Palliative Treatment.—Most medical students and young physicians have small patience with palliative treatment since it is designed only to relieve suffering or prolong life without offering hope of cure. However, in one sense, no physician ever saves a life, he only postpones a death, and he does well to recognize that much of his most valuable work is palliative.

Radiation therapy as a palliative agent has given months and years of useful life to innumerable patients with incurable cancer and has eased the suffering of countless more. Palliative radiation is useful in a wide range of neoplasms including many which are classed neither as radiosensitive nor radiocurable. Radiation is the primary form of treatment in most cases of Hodgkin's disease, chronic leukemia, and lymphoma. These neo-

plasms, though practically incurable, are radiosensitive and often show striking and prolonged remissions. Certain tumors, such as carcinoma of the breast, are only moderately sensitive to radiation. However when surgery is not feasible because of the extent of the growth or the condition of the patient or when the growth recurs after surgery, radiation therapy offers worth-while palliative benefits and even an occasional cure. The excruciating pain of primary or metastatic cancer in bone is frequently ameliorated by irradiation. This effect is difficult to explain since it can occur even in such radioresistant tumors as osteogenic sarcoma and sometimes appears within a few hours following treatment before

significant gross or histologic changes in the tumor can be detected. A considerable number of neoplasms including malignant melanomas and carcinomas of the lung, stomach, liver, and pancreas show little palliative response to irradiation.

ATOMIC BOMB INJURIES

The achievement of nuclear fission by chain reactions has introduced both in peace and in war a general hazard of radiation injuries never before present in the world. If the nucleus of certain heavy atoms including uranium and plutonium is struck by a neutron of suitable energy, the nucleus splits to yield new elements of lower atomic number. As a by-product of each nuclear fission, enormous amounts of free energy are released. Part of the energy is in the form of neutrons which on striking neighboring atoms cause fission in them and release more neutrons to continue the chain. In the atomic pile the rate of the reaction is controlled by introducing into the fissionable mass, material which will absorb neutrons. The absorbed neutrons are removed from "reproduction," as it were, leaving behind only a sufficient number to maintain a stable rate of fission. The atomic bomb is a modified atomic pile in which the reaction is unrestrained and builds up in a geometric crescendo of intensity.

The biologic effects of the atomic bomb explosions over the Japanese cities of Hiroshima and Nagasaki during World War II can be understood only in terms of the varied forms in which the tremendous energy of the explosion was released. Full information is not available, but the following list includes most of the important components:

1. Blast
Estimated at Hiroshima to equal the detonation of 20,000 tons of T.N.T.
2. Electromagnetic radiation.
Probably a fairly complete spectrum with notable intensity of short gamma rays, visible light and infrared (heat) rays.
3. Particulate radiation.
Neutrons, electrons (beta particles), and others.
4. Radioactive fission products.
The nuclear residue of the fissioned atoms is made up of a group of almost 200 intensely radioactive isotopes with approximate atomic numbers ranging from 30 to 63, having short and long half-lives and emitting different types and intensities of radiation.
5. Secondary or induced radioactivity.
The neutrons and some of the gamma rays carry sufficient energy to disrupt atoms and induce radioactivity in matter (including human bodies) which absorbs them.

Survivors in the Japanese cities described an instantaneous, blinding flash of white or green light, accompanied by intense heat and preceding the shock wave of the detonation. The mechanical blast was responsible for demolishing

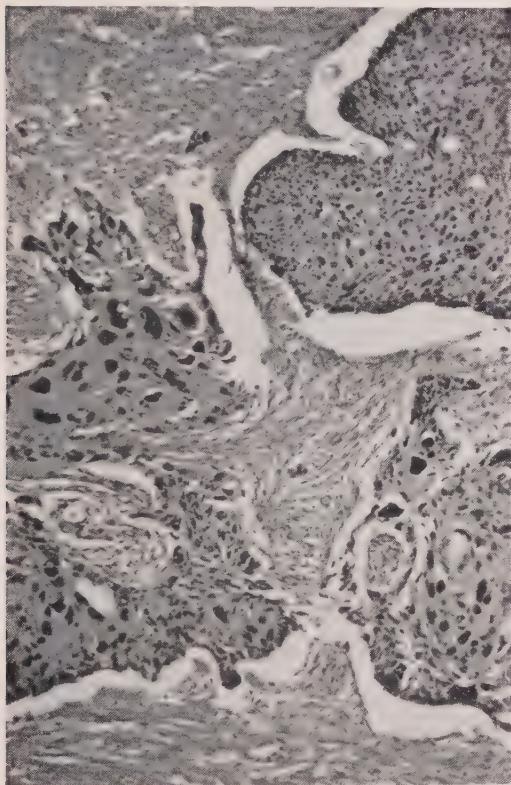


Fig. 126.—Photomicrograph of an advanced carcinoma of the cervix ten months after unsuccessful combined roentgen-ray and radium treatment. The tumor tissue in the right upper corner is composed of small fairly uniform cells resembling the pretreatment biopsy. This nest of cells shows no obvious radiation changes and probably proliferated subsequent to the treatment. In all other regions the tumor contains some cells that appear nonviable and many bizarre cells with large, irregular, pyknotic nuclei. Such changes which are consistent with radiation injury, suggest that these nests of tumor were present at the time of treatment.

most of the houses in the cities and was forceful enough to break windows at a distance of 10 miles. The flash, of course, was electromagnetic radiation in the visible range and the heat was due to a large component of infrared with some probable contribution from ultraviolet and visible rays. The heat lasted only about 3 seconds but was so intense that unprotected human skin directly exposed to the flash was burned or charred within a radius of 4,000 yards of the ground center of the explosion. The heat did not envelop objects like a blast of hot gas but affected only those surfaces facing in the direction of the explosion.

Survivors of the blast and the heat flash had no way of knowing that in the same instant they had been exposed to a discharge of ionizing radiation and many who later died believed at first that they had escaped unharmed. The intensity and penetration of the neutron and gamma ray discharge is illustrated by the fact that in the three-story, concrete Red Cross Hospital at Hiroshima, 2,000 yards from the ground center of the explosion, x-ray films stored in a lead vault were exposed and ruined.

Residual radiation from fission products of the bomb did not play an important part in causing human injuries. In atomic explosions

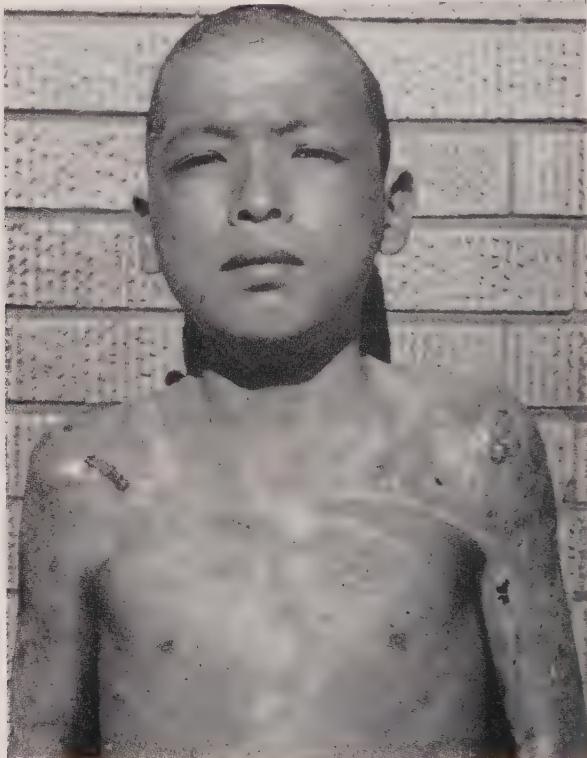


Fig. 127.—Flash burns from atomic bomb. This 15-year-old Japanese boy was standing in the open at 5,250 feet from the ground center of the explosion, bare to the waist, watching the United States planes. The flash burns on his chest are partially healed but there are several areas of excess granulation tissue. (Photograph by courtesy of the Medical Division, The United States Strategic Bombing Survey.)

Any person, or any part of the body shadowed from the light of the explosion was equally protected from the heat. This radiation had little penetrating power as shown by the fact that skin was adequately protected by a thin covering of cloth. The Japanese estimated that the momentary temperature on exposed surfaces within 500 yards of the ground center reached 1200° to 2000° C. and it is thus easy to understand why flash burns accounted for a large proportion of the early casualties and deaths. It is estimated that mechanical and thermal injuries accounted for about 85 per cent of the casualties while only 15 per cent were due primarily to ionizing radiation.

over land or water most of the fission products are blown high into the air as radioactive dust and vapor and do not settle in dangerous concentrations unless they are carried down by rain. By contrast, in the underwater explosion at Bikini 99 per cent of the fission products were trapped in water and were prevented from disseminating so widely in the atmosphere. As a result the area remained uninhabitable for some time.

Radioactivity secondarily induced within human bodies or other objects at Hiroshima and Nagasaki did not appear to be of great importance. None who entered the city for the first time after the explosion suffered any radia-

tion effects and determinations by the Japanese on the bodies of a few dead horses and men showed very little residual radioactivity several weeks after the explosion.

Radiation sickness appeared in many victims within an hour and was characterized by fever, nausea, vomiting, and watery or bloody diarrhea. Characteristic lymphopenias and leukopenias developed promptly and often persisted for weeks before death or recovery took place. Anemias developed more slowly and were either progressive or showed a slow recovery. In fatal injuries, whether death occurred in the early or later periods, a terminal rise in temperature was characteristic and extensive ecchymoses and hemorrhages were often present in the viscera, skin, and other structures. The

Injury to the genital system was limited essentially to the testes in men and the ovaries in women. One hundred twenty-four men were examined three to four months after exposure. Thirty-five per cent were sterile (less than 5,000 spermatozoa per cubic millimeter of ejaculate) and a high percentage of abnormal spermatozoa were present in the seminal fluid of both sterile and nonsterile men. In a group of 399 sexually mature women only 30 per cent continued to menstruate regularly. Eighty per cent of those with early suppression of menses began to menstruate normally within two to six months and several subsequently became pregnant. Since the testes and ovaries are so vulnerable to radiation injury, it might seem strange that the incidence of sterility was so

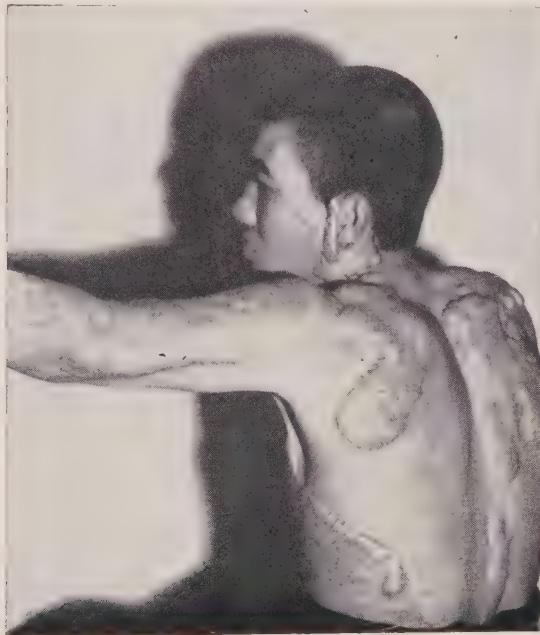


Fig. 128.—Keloids complicating healed flash burns from the atomic bomb. This man was standing with his back to the blast and his left arm behind him, leaning on a shovel. The portion of the left posterior thorax that was shielded by his arm is not affected, but in many other areas the flash burns have healed with the formation of massive keloids. Keloids may follow any extensive burn and were common among the bomb victims. It has not been shown that ionizing radiation was a factor in keloid formation. (Photograph by courtesy of Dr. Austin M. Brues.)

bleeding could not always be explained by thrombocytopenia and is believed to have been due in part to the presence of a heparin-like substance in the circulating blood. Secondary bacterial infection was a frequent and serious complication in patients with leukopenia and agranulocytosis. Persons less heavily irradiated often felt well for several days or weeks. Many then developed the lassitude, anorexia, and weakness characteristic of radiation cachexia. Associated anemia, leukopenia, and hemorrhagic manifestations were often present. Death from leukopenia was most common in the first week or two, hemorrhagic deaths reached a peak from the third to the sixth week, and after the second month radiation cachexia and anemia accounted for the greater proportion of deaths.

low in both sexes. However, a dose of some 500 roentgens delivered to the gonads is necessary to produce permanent sterilization, and since this same dose applied to the whole body usually proves fatal, most of the surviving men and women were subjected only to substerilizing exposures. For the same reason delayed erythema of the skin was not encountered in survivors, but reactions characteristic of suberythema doses, such as temporary epilation, did occur.

Radiation injuries from the atomic bomb differed from ordinary radiation injuries chiefly in this one respect. Those who lived long enough to develop progressive tissue changes had not been subjected to local tissue doses much in excess of 500 r, a dose which is much

too small to produce significant damage in any of the radioresistant structures. Profound radiation changes were largely confined to the highly radiosensitive tissues—the blood and blood-forming organs, the gastrointestinal mucosa, and the gonads. The pathologic changes in these tissues were qualitatively identical with those resulting from local treatment with roentgen rays and therefore need not be described again. The limiting factor in survival was the severity of the systemic reactions rather than local tissue injury.

References

General Reviews

- Duggar, B. M.: *Biological Effects of Radiation*, New York, 1936, McGraw-Hill Book Co.
- Colwell, H. A.: *The Method of Action of Radium and X-rays on Living Tissues*, London, 1935, Oxford University Press.
- Crowther, J. A.: *Brit. J. Radiol.* **11**: 132, 1938.
- Lea, D. E.: *Actions of Radiations on Living Cells*, London, 1947, Cambridge University Press.
- Warren, S.: *Arch. Path.* **34**: 443, 562, 749, 917, 1070, 1942; and **35**: 121, 304, 1943.

Radioactive Isotopes

- Hahn, P. H.: *Radioisotope Therapy*, New York, 1951, Academic Press.
- Hevesi, G.: *Radioactive Indicators*, New York, 1948, Interscience Publishers.
- Kamen, Martin D.: *Radioactive Tracers in Biology. An Introduction to Tracer Methodology*, ed. 2, New York, 1951, Academic Press.
- Morrison, A., Dixon, W. R., Garrett, C., Johns, H. E., Bates, L. M., Epp, E. R., Cormack, D. V., and Fedoruk, S. O.: *Science* **115**: 310, 1952 (radioactive cobalt).
- Symposium. Diagnostic and Therapeutic Uses of Radioactive Isotopes, *Brit. J. Radiol.* **23**: 527, 1950.

Infrared Visible and Ultraviolet Rays

- Blum, H. F.: *Physiol. Rev.* **25**: 483, 1945 (effects of sunlight on man).
- Laurens, H.: *The Physiological Effects of Radiant Energy*, American Chemical Society, Monograph Series, New York, 1933, Chemical Catalogue Co.

Radiosensitivity

- Brues, A. M., Marble, B. B., and Jackson, E.: *Am. J. Cancer* **38**: 159, 1940 (effects of colchicine and radiation).
- Desjardins, A. U.: *Am. J. Roentgenol.* **32**: 493, 1934 (radiosensitivity of tumors).
- Evans, T. C., Goodrich, J. P., and Slaughter, J. C.: *Radiology* **38**: 201, 1942.

Skin

(See Warren, *General Reviews*.)

- Wolbach, S. B.: *J. M. Research* **21**: 415, 1909.

Gastrointestinal Tract

- Friedman, N. B.: *Arch. Path.* **34**: 749, 1942.

Lung

- Warren, S., and Spencer, J.: *Am. J. Roentgenol.* **43**: 682, 1940.

Bone and Cartilage

- Gates, O.: *Arch. Path.* **35**: 323, 1943.
- Martland, H. S.: *Am. J. Cancer* **15**: 2435, 1931.

Blood and Blood-Forming Organs

- Allen, J. G., and Jacobson, L. O.: *Science* **105**: 388, 1947.
- Dunlap, C. E.: *Arch. Path.* **34**: 562, 1942.
- Jacobson, L. O., Simmons, E. L., Marks, E. K., Robson, M. J., Bethard, W. F., and Gaston, E. O.: *J. Lab. & Clin. Med.* **35**: 746, 1950.
- March, H. C.: *Radiology* **43**: 275, 1944 (leukemia in radiologists).
- Minot, G. R., and Spurling, R. G.: *Am. J. M. Sc.* **168**: 215, 1924.

Reproductive Organs and Reproduction

- Henshaw, P. S.: *J. Nat. Cancer Inst.* **1**: 789, 1941.
- Lorenz, E., Heston, W. E., Eschenbrenner, A. B., and Deringer, M. K.: *Radiology* **49**: 274, 1947.
- Miller, J. R., Corscaden, J. A., and Harrar, J. A.: *Am. J. Obst. & Gynec.* **31**: 518, 1936.
- Murphy, D. P., and Goldstein, L.: *Am. J. Roentgenol.* **22**: 207, 1929.
- Peck, W. S., and McGreer, J. T., with Kretzman, N. R., and Brown, W. E.: *Radiology* **34**: 176, 1940.
- Warren, S.: *Arch. Path.* **35**: 121, 1943.

Atomic Bomb Effects

- Allen, J. G., Moulder, P. V., and Enerson, D. M.: *J. A. M. A.* **145**: 704, 1951.
- Brues, A. M., Henshaw, P. S., Block, M. A., Neel, J. V., and Ulrich, F. W.: *General Report. Atomic Bomb Casualty Commission*. Washington, D. C., 1947, National Research Council.
- Cogan, D. G., Martin, S. F., and Kimura, S. J.: *Science* **110**: 655, 1949.
- Hershey, J.: *Hiroshima*, New York, 1946, Alfred A. Knopf, Inc.
- Le Roy, G. V.: *J. A. M. A.* **134**: 1143, 1947.
- Liebow, A. A., Warren, S., and DeCoursey, E.: *Am. J. Path.* **25**: 853, 1949.
- The Medical Division, United States Strategic Bombing Survey: *The Effects of Atomic Bombs on Health and Medical Services in Hiroshima and Nagasaki*. Washington, D. C., 1947, U. S. Government Printing Office.
- United States Atomic Energy Commission, *The Effects of Atomic Weapons*, Washington, D. C., 1950, U. S. Government Printing Office.
- Warren, S.: *Cancer Research* **6**: 449, 1946.
- Warren, S., and Draeger, R. H.: *U. S. Nav. M. Bull.* **46**: 1349, 1946.

Miscellaneous

- Dunlap, C. E.: *Occupational Med.* **1**: 237, 1946.
- Glasser, O.: *Medical Physics*, Chicago, 1944, Year Book Publishers.
- Prosser, E. E., Lisco, H., Brues, A. M., Jacobson, L. O., and Swift, M. N.: *Radiology* **49**: 299, 1947.
- Packard, C.: *Quart. Rev. Biol.* **6**: 253, 1931.
- Tobias, C. A.: *Federation Proc.* **10**: 595, 1951 (mechanism of action).

Chapter 9

GENERAL PRINCIPLES OF INFECTION AND RESISTANCE

PAUL R. CANNON

The effects of microbial growth, whether due to bacteria, animal parasites, viruses, or rickettsias, are as varied as the infections causing them. It is essential, therefore, that students of pathology acquire some familiarity with the biologic principles which influence microbial growth in tissues and the immunologic mechanisms which counteract it; for upon the ability of microorganisms to grow depend the pathologic consequences of parasitism. In this discussion consideration will be given mainly to the problem of bacterial growth in the animal body.

Bacteria, in general, tend to grow outside of cells, for the most part in the intercellular fluids. Here, presumably, they are best able to secure nutrient substances essential for their metabolic needs; indeed, their adaptability to the host environment and their survival depend upon their capacity to utilize these food materials. It should be noted, however, that some bacteria may also grow intracellularly. Under such circumstances conditions influencing their growth proclivities are less well defined and presumably resemble more closely those operating with respect to viruses.

The pathogenic effects of bacterial infection, on the other hand, depend in many instances upon characteristics inherent in the bacteria themselves. For example, some bacteria, such as staphylococci, tend to grow in clusters rather than as single organisms; others, as some varieties of streptococci, meningococci, and gonococci, release products which cause edema, inhibit the clotting mechanism, or act as so-called "spreading factors" which favor diffuse bacterial spread through the tissues and ultimately into lymph channels and the circulating blood. Some mobile microorganisms, notably typhoid bacilli and spirochetes, may also spread diffusely by virtue of their motility; other microorganisms, although localized in infected areas, secrete toxins which are absorbed and produce their characteristic toxic effects, for example, diphtheria and tetanus bacilli. Others elaborate so-called leukotoxic substances which promote the accumulation of leukocytes around the bacteria. In these and other ways the extent of an initial bacterial localization may be influenced distinctively because of attributes possessed by the bacteria themselves. If the bacteria spread freely through the tissues they are called invasive; if they grow readily and disseminate to induce disease they are called virulent; if they elaborate poisons or exotoxins they are toxicogenic. In any case these terms serve merely to describe potentialities characteristic of particular microorganisms; they are

useful, however, in helping to explain differences in bacterial behavior manifested by infections of varying kinds.

ANTIMICROBIC RESISTANCE

The most favorable consequence of an adequate resistance is a speedy termination of microbial growth, thereby preventing bacterial dissemination and minimizing tissue injury. This usually depends upon the effective functioning of three processes, viz., (1) primary phagocytosis; (2) phagocytosis complementary to immune body action, and (3) the action of antibiotic mechanisms in the tissues which restrict bacterial growth. Immunology is concerned with all of these aspects of infection in many ways, as manifested by varied tissue reactions in differing states of natural and acquired resistance.

These varying tissue reactions often cannot be investigated adequately in human disease because they are frequently at an end-stage when examined pathologically. In order to learn about the sequence of events in earlier phases of microbial growth in tissues it is necessary to produce in experimental animals so-called "model infections" under various conditions of resistance and for varying periods of time in order to make a sequential study of the inhibitive action of immunologic mechanisms upon bacterial growth. In this way it is possible to establish certain general principles which can be applied to somewhat analogous conditions seen in human infections.

Some Modifying Principles of Resistance.—The extent of bacterial infection is determined and modified by conditions inherent in the host, such as age, sex, heredity, nutritional states, metabolic abnormalities, and the functional integrity of mesenchymal tissues of the bone marrow, reticuloendothelial system, and elsewhere.

The Influence of Age Upon Resistance to Bacterial Infection.—It is a generally accepted fact that antibacterial resistance often tends to be less effective at the extremes of life. For example, in infants and young children, after the immune substances, acquired from the mother have been in large part utilized, the so-called childhood infections tend to appear. In the course of these a child develops specific immunities to a variety of pathogenic bacteria, thereby acquiring resistance which may persist for months or years. At times, however, a child fails to resist infections effectively, due, among other causes, to massiveness of infection, overpowering bacterial virulence, or for other

reasons. Such types of infection may then become generalized, and at times lethal, as, for example, in childhood tuberculosis or rheumatic disease. The outcome depends presumably upon the capacity of mesenchymal tissues to fabricate phagocytes and immune substances in quantities adequate to cope with the microbial invaders. This ability in turn may be affected also by hereditary influences, nutritional and other factors, and by the developing tempo of the inflammatory reaction.

Similarly in old age resistive mechanisms once adequate may gradually deteriorate and for varied reasons. Thus in senescence there is a slowing down of metabolic processes essential for the adequate production of phagocytic cells and immune substances. When pathogenic microorganisms enter tissues of aged individuals whose mesenchymal tissues have become atrophic, the mobilization of phagocytes and antibodies may be too slow to ensure a speedy localization of an incipient infection. This is particularly true in pulmonary infections where edema, favored by myocardial weakness or hypostasis, may provide conditions exceptionally conducive to microbial growth. Thus it is not surprising that pneumonia so frequently brings life to an end as the so-called terminal pneumonia.

The Influence of Nutrition Upon Bacterial Resistance.—All pathogenic microorganisms are foreign proteins; and after they have entered living tissues they must be assimilated by the processes of protein metabolism. Therefore, both from the standpoint of the host and of the bacteria, nutrition can influence bacterial growth, favorably or unfavorably, whether by virtue of the quantity and quality of phagocytic cells mobilizable, by the action of specific immune substances, or by the content of growth accessory materials in the tissues.

The effects of profound malnutrition or undernutrition illustrate the close relationship which has often been observed between severe starvation and increased susceptibility to bacterial infection. Similarly, persons afflicted with debilitating diseases associated with severe starvation are also frequently susceptible to chance infections, particularly when subjected to poor hygienic conditions. Moreover, it has been shown both clinically and experimentally that a severe degree of inanition leads to vitamin deficiencies and to depletion of tissue-protein reserves, thereby affecting both the ability of bacteria to grow and of the mesenchymal tissues and immune substances to counteract this growth. Thus severe debilitation leads eventually to bone marrow atrophy as well as to atrophy of lymph nodes, lymphoid tissues, spleen, etc., thereby reducing the total reserve of phagocytic cells available at a time of need to respond to a developing infection. Concomitantly, depletion of the protein and vitamin stores tends to reduce the potentiality of the antibody-producing tissues to fabricate immune bodies effectively and of tissues in general to synthesize protein. In these and other ways good nutrition presumably favors resistance to infection whereas poor nutrition tends eventually to lessen it.

The Role of Altered Metabolism in Resistance to Infection.—Bacterial growth in tissues may

be modified or altered by metabolic conditions which interfere with resistive mechanisms ordinarily operative. Thus the increased susceptibility to infection resulting from alcoholic intoxication has long been recognized, notably in pneumonia. Evidence indicates that this decreased resistance may be due in large part to the toxic, paralysant action of alcohol upon neurovascular mechanisms concerned in inflammation, and because of this, circulating leukocytes may assemble tardily around the bacterial agents, allowing the latter more time in which to grow. In active diabetes, the altered carbohydrate metabolism associated with high sugar concentrations in tissues may afford a better environment for bacterial growth, explaining, in part at least, the well-known tendency of diabetic patients to develop suppurative and other infections. It is recognized, however, that other mechanisms may also be operative as well. The tendency of patients with hemochromatosis to develop intercurrent infections may similarly be related to hepatic disease and a deranged carbohydrate metabolism. In lipid nephrosis, in which there is a marked loss of plasma protein through the kidneys and a concomitant severe hypoproteinemia, there is an enhanced tendency for the patient to develop spontaneous pneumococcal or streptococcal bacteraemia or peritonitis. Here the profound loss of plasma globulins, particularly of the antibody-containing portion of these blood proteins, together with reduction of the globulin reserves in association with atrophy of mesenchymal tissues may account in part for the loss of resistance. In these and other ways altered metabolism may influence general mechanisms normally responsible for effective resistance to bacterial growth.

Phagocytosis in Resistance to Bacterial Infection.—Of all the immune processes responsible for effective natural resistance to bacterial infection, phagocytosis must be accorded a foremost role. Some pathologists maintain, indeed, that in natural resistance phagocytosis is the most fundamental process and that even in acquired resistance it is the most effective. At any rate the development of the concept of phagocytosis constitutes one of the great biologic ideas of the past century and its significance should not be underestimated.

When Metchnikoff first described the phagocytes he considered them as small digestive "glands" which could engulf foreign substances and destroy them by the process of intracellular digestion. He concluded, also, that during this digestion specific immune substances arose which were liberated into the circulating fluids. In mammals the smaller phagocytic cells arise principally from the bone marrow. These are called granulocytes or polymorphonuclear leukocytes. Because of their mobility and availability they tend to congregate around an area of injury, and, by means of their phagocytic ability, to engulf the injurious agent, neutralize its toxic action, or destroy it. So long as their active production in the bone marrow proceeds uninterruptedly they serve as potent defensive mechanisms, and it is only when they fail to be supplied continuously in time of need, as, for example, after severe bone marrow depletion or injury, because of which the primitive myelo-

blasts stop forming mature leukocytes at the normal rate, as in the so-called "maturation arrest" of acute granulocytopenia, that the numbers of circulating leukocytes become inadequate. The lethal effects of severe radiation injury are often due to infection resulting from this leukotoxic action on the hematopoietic system. Likewise some of the newer chemotherapeutic drugs used in the treatment of neoplastic disease may cause a similar injury to the bone marrow. The reduction in the number of available circulating leukocytes, termed leukopenia, thus indicates a failing mechanism of defense. In general, therefore, leukocytosis (increase in the actual number of circulating leukocytes) indicates a favorable prognosis whereas, conversely, leukopenia suggests a bad prognosis.

It is obvious, however, that the phagocytic mechanisms are nonspecific and that at times their effectiveness is inadequate. Otherwise there would be no need to attempt to develop acquired immunity against many types of bacteria which tend to induce generalized infections, such as typhoid fever, etc. Nevertheless some maintain that primary bacterial localization depends largely upon such nonspecific inflammatory mechanisms whereby fibrin is deposited quickly around the bacteria, thrombosis of lymphatics occurs, and the bacteria are thereby "sealed in" by the formation of a mechanical barrier around the infective agents. According to this concept, the more violent and intensified the inflammatory reaction, the more effective should be the bacterial localization. Although it is well known that in the later stages of inflammation there is frequently developed a barrier of cells and fibrin, the so-called "pyogenic membrane," the important question is: Does this membrane develop immediately in inflammation and soon enough to prevent bacterial spread to the lymphatic channels and blood?

It should be pointed out that there are serious objections to this point of view. In the first place, it has long been known that one of the earliest manifestations of inflammation is an increased outflow of lymph from the area of inflammation. This does not bespeak a massive thrombosis of lymphatic channels. Again, it has been shown that experimentally produced inflammation cannot protect an animal against pathogenic microorganisms introduced into the area of inflammation at the beginning of the process. Experiments in which inflammation is produced by a violent irritant, followed considerably later by the infectious agents obviously do not simulate conditions of natural infection. Moreover, it has been shown that when tubercle bacilli are injected into the skin of a susceptible guinea pig and a resistant cat, an intense inflammatory reaction develops in the former and a negligible one in the latter. In this instance, therefore, it might even be said that resistance varies inversely with the degree of intensity of the inflammatory response. No resistive mechanism can be considered adequate unless it can protect against highly invasive microorganisms, for, obviously, one cannot incur infection selectively and choose only those types of infective agents which can be readily localized at the portal of entry.

One of the most dramatic facts of immunology is the demonstration of the conversion of an animal, normally so susceptible to a particular microorganism that a few microbes injected into the skin will induce a fatal bacteremia in the course of a day or two, into one resistant to the injection of thousands of the same types of living virulent microorganisms, merely by active immunization with a vaccine prepared from these microorganisms or by the injection of an antiserum which is specific for them. Whereas in the absence of specific immunity intradermal injection of such a virulent microorganism, as, for example, a virulent pneumococcus into a susceptible rabbit, is followed by a large, hemorrhagic edematous spreading local lesion, with septicemia and death, a similar injection into an immune rabbit is followed by the development of a minimal localized lesion, without bacterial generalization or any serious general consequences. When such lesions are examined microscopically it can be seen that in the non-immune tissues the microorganisms grow profusely, spread quickly to the contiguous tissues, and, despite the inflammatory response, there is little if any phagocytosis or walling off of the inflammatory focus. On the other hand, in immune tissues, the bacteria grow sparsely, tend to adhere to one another and to the immune tissues, not infrequently tend to agglutinate, and are abundantly phagocytosed and then destroyed. This phenomenon has been observed experimentally in infections produced by staphylococci, pneumococci, tubercle bacilli, and other types of pathogenic microorganisms.

In any type of bacterial infection, therefore, it is obvious that the pathologic consequences must depend upon the effectiveness with which the defensive processes of the host can bring about the speedy termination of microbial growth. If bacterial growth is quickly stopped there will be no toxin production, no liberation of fibrinolytic substances, no edema, and no microbial spread by contiguity to the lymph channels and blood. Conversely, in the absence of an effective antibacterial defense, many kinds of pathogenic microorganisms may proliferate freely in the tissues and spread widely to induce a diffuse initial lesion, blood stream invasion, metastatic infection, or even death. In general it is true that an effective resistance is characterized by the development of a local lesion with but slight tendency for the microorganisms to disseminate, whereas in the absence of an effective resistance the initial lesion may be minimal and the bacterial dissemination maximal. From the viewpoint of pathology the problem is to secure conditions favoring the former type of host response.

In natural resistance the localizing capacity of the infected individual depends largely upon the speed and effectiveness of the inflammatory reaction in mobilizing in the area of bacterial injury the phagocytic cells and humoral elements (fibrinogen, enzymes, natural antibodies, oxygen, and minerals and possibly vitamins) essential for the termination of bacterial growth. One of the earliest manifestations of inflammation is the increased permeability of blood vessels as a consequence of

which both cellular and fluid elements may leave the blood vessels and help to counteract microbial damage. Any agency which tends to hamper this favorable response tends also to encourage bacterial growth. Moreover, time allowed for growth affords an added opportunity for the bacteria to liberate harmful substances which may enlarge the area of infection to be encompassed by the inflammatory process.

The Importance of Fever in Resistance to Bacterial Infection.—The role of fever in infection has been an enigma for many years, but whether it is essentially beneficial or harmful is still a matter of uncertainty. Fever is presumably an accompaniment of a state of general cellular excitation in which the "heat centers" are so affected as to change the apparatus controlling heat loss. The question is, are the effects of fever due to fever per se or is fever merely an accompaniment of these other effects?

For a long time fever was looked upon as a protective mechanism, the development of which should be encouraged; later the view developed that it was basically a harmful process and should be restricted whenever possible by the use of so-called antipyretic drugs; today the dominant opinion is that fever, in general, acts beneficially but that if too prolonged or too severe, it may at times be harmful. Here, too, however, one must recognize the difficulty of dissociating the effects of fever from those of the condition which causes the fever.

There is evidence suggesting that fever is frequently a beneficial accompaniment of infectious states. For example, some microorganisms cannot grow effectively at elevated body temperatures, for example, above 39° to 40° C. Thus the spirilla of relapsing fever have been found to lose motility at this temperature, some pneumococci lose virulence, and some gonococci, streptococci, and pneumococci are less able to grow in tissues at febrile temperatures. Experiments have indicated that phagocytosis also may be more effective at a temperature between 37° and 40° C. and that antibody production may also be accelerated. Recent evidence, however, has tended to suggest caution in this regard because experiments have even shown that hyperpyrexia may at times depress antibody production and even lead to an accelerated destruction of antibodies already formed. In fever there is a tendency for hyperplasia of the bone marrow and lymphoid tissues to develop, although here again the infectious agent may be responsible and not the fever per se. Nevertheless, when individuals have been subjected to high temperatures, as after the injection of foreign proteins, induced malaria, or in the hyperthermic apparatus, clinical improvement has been secured occasionally in patients with such chronic infections as syphilis of the central nervous system, chronic arthritis, etc.

Prolonged fever, on the other hand, may be accompanied at times by harmful consequences. Thus the protein breakdown accompanying the febrile state is somewhat comparable to starvation. In prolonged fever the increased metabolic rate with the utilization of the labile protein reserves and the loss of nitrogen through the urine may lead in time to severe weight loss and

tissue depletion. Under these circumstances the problem of inanition may become more important than that of the effects of the fever-producing agent itself. High fever also may lead to severe parenchymatous degeneration of such organs as the heart, liver, kidneys; it may, through its stimulation of heart action, lead to myocardial exhaustion, and it may, in severer forms, even lead to anoxic cerebral lesions. It may also profoundly reduce the capacity of an individual to fabricate blood proteins, including hemoglobin.

In summary, it is probable that fever cannot be looked upon entirely as a protective mechanism; nevertheless, the general state of cellular excitation accompanying fever seems to be an expression of a greater tissue reactivity which is more often beneficial than harmful. It is only in the severer grades of fever and after prolonged hyperpyrexia that the adverse effects are manifested.

ANTIBIOTIC AND CHEMOTHERAPEUTIC AGENTS IN BACTERIAL DEFENSE

The introduction of the antibiotic drugs has tended to divert attention to some extent from the more purely immunologic mechanisms of defense. It should be borne in mind, however, that, despite the tremendous value of these drugs, they operate for the most part *a posteriori*, that is, after an infection has developed. Furthermore, because of the fact of speedy termination of infection by the antibiotics, little residual specific immunity persists as a sort of compensatory recompense for the infection. Such a lessened residual immunity may consequently carry with it a biologic disadvantage in that it may favor the chances of recurrence of infection. For example, a tendency to relapse occasionally seen in typhoid patients who have been treated with antibiotic drugs has suggested to some the idea of employing "interval therapy" in order to encourage a controlled mobilization of the forces of active immunity during the course of the disease. There is little prospect as yet, also, of using these agents for the prevention of infections which may now be largely prevented by prophylactic immunization, such as typhoid fever, yellow fever, typhus, cholera, diphtheria, tetanus, smallpox, etc.

It is now apparent that the antibiotic drugs exert their beneficial effects mainly through their ability to influence microbial growth rather than through a direct action on the defense mechanisms of the host. In other words, their action is essentially bacteriostatic, most probably due to their competitive ability to combine with bacteria and thus prevent the latter from utilizing substances somewhat similar chemically but nutritively essential, as, for example, para-aminobenzoic acid. At any rate, they are not protoplasmic poisons in a general sense and apparently do not kill bacteria directly. In short, they require the complementary action of phagocytes in order to eliminate the infectious agents.

In the utilization of these drugs it is also obvious that early administration is essential if they are to reach the area of bacterial injury

before it has become partially walled off by the inflammatory process. Otherwise there may be an increasing interference with the passage of the drugs from the blood stream into the locus of infection.

A provocative question raised by the prolonged protection of large masses of people against infection by the widespread use of antibiotics is that of the possible consequences to individuals later on who become infected by strains of microorganisms which are resistant or have become resistant to antibiotic agents. For instance, there is growing evidence, particularly with respect to staphylococci and gonococci, of an increasing incidence of penicillin-resistant strains. As yet, no prediction can be safely made concerning a final answer to this question.

In recent years renewed attention has been given to the possible role of the adrenal steroids in infection and resistance. The spectacular effects at times following administration of

ACTH or cortisone have suggested the possibility that these materials might favorably influence basic immunologic mechanisms. This suggestion, however, has not as yet been substantiated. Although it is true that these drugs may at times depress pain, fever, sedimentation rate, and eosinophile count, it is also apparent that they may adversely influence wound healing, retard the inflammatory response, and cause a depression of antibody output. They may also induce a negative nitrogen balance and a disturbed carbohydrate metabolism. To date, therefore, the indications for their therapeutic use in infection are not clearly defined; moreover, in some instances they have apparently favored the development of serious infections by obscuring important symptoms, such as pain and fever. In the light of these facts it is obvious that more information must be gained before the relationship of these steroids to the mechanisms of immunity can be properly evaluated.

Chapter 10

BACTERIAL DISEASES

HOWARD C. HOPPS

INTRODUCTION AND GENERAL PRINCIPLES

Bacterial Disease Contrasted With Inflammation per se

Infectious lesions are inflammatory lesions and all the fundamental principles which concern the body's reaction to injury are strictly applicable to them. An immense number of sterile substances, both fluid and solid, soluble and relatively insoluble, incite a reaction essentially similar to that which follows the invasion of microorganisms. The same is true of physical agents. Any special features of bacterial disease thus depend upon certain peculiarities of the inflammatory stimulus:

1. *Unlike purely chemical or physical inflammatory agents bacteria can proliferate within the body, thus affording a prolonged, continuous stimulus for inflammatory reaction.*

This property explains why a few pathogenic microorganisms, infinitesimal as a stimulus in themselves, can produce an overwhelming disseminated infection and death in so short a time as eight to twelve hours. It is largely on the basis of this ability to reproduce themselves within the host that bacteria are considered invasive, virulent, or pathogenic. The most important defense against bacterial disease is prevention of this bacterial multiplication, hence the effectiveness of bacteriostatic agents such as penicillin and sulfonamides.

2. *As a result of bacterial proliferation within the body, bacterial lesions may spread in a manner quite unlike that which occurs in the case of non-living inflammatory agents.*

The very act of proliferation accomplishes spread of some degree, a spread by contiguity. Wider extension occurs through the action of toxins elaborated by the bacterium, toxins that produce edema, dissolve fibrin, or dissolve the ground substance which normally maintains structural integrity of tissues (spreading factor).

3. *Bacteria elaborate a variety of inflammatory agents and, in addition, certain*

substances which modify the body's "normal" inflammatory response.

The precise mechanism by which bacteria produce death of cells is obscure, but the bulk of evidence indicates a chemical (toxic) basis for such injury. In order for some bacteria to kill, it is necessary that they become widely disseminated and that they affect many tissues directly. Other organisms can exert a lethal effect while localized to a small area, because the potent toxins which they elaborate are absorbed, widely distributed and produce a toxic effect on cells remote from the site of origin.

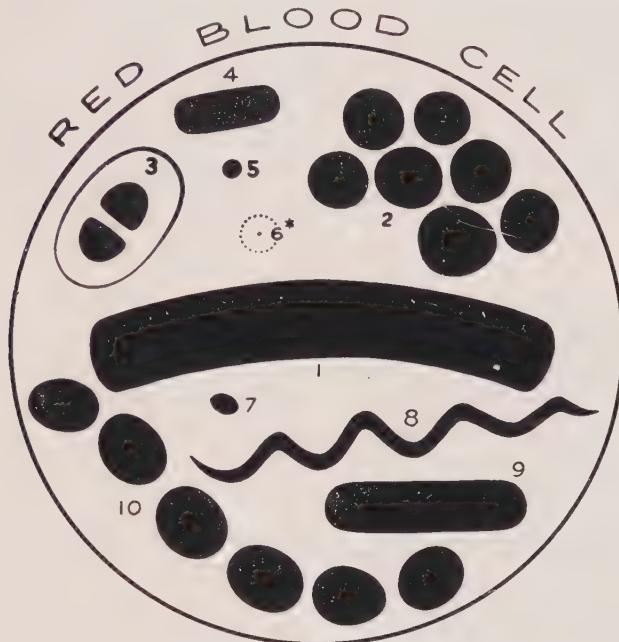
Those toxins which actually destroy tissues, the necrotoxins, are numerous and varied. They exert their effect in many ways, all of which must ultimately concern the blocking of vital enzymatic processes within the cell. In addition to these necrotoxins there are a host of others which do not destroy tissues directly, but nevertheless profoundly affect the inflammatory response and thus affect bacterial invasiveness and pathogenicity. The importance of some of these warrants a brief individual consideration.

"*Spreading factors,*" notably hyaluronidase, have been studied in great detail especially by Duran-Reynals. Hyaluronidase acts to dissolve the intercellular cement or ground substance, hyaluronic acid, which is largely responsible for the adherence of individual cells to one another. In this manner, particulate matter of bacterial size is allowed to spread between the individual cells of a tissue, without respect for tissue integrity. Pathogenic staphylococci are particularly rich in this substance. The extent to which staphylococci elaborate hyaluronidase tends to parallel directly their capacity to produce disease. The action of this spreading factor on India ink (particulate carbon of approximately the same size as staphylococci) is illustrated in Fig. 130. *Edema-producing factors* are important because they too separate tissue elements allowing microorganisms to drift passively through various tissue spaces, carried by a fluid medium. Furthermore, the protein substance of the edema furnishes bacterial nutriment and serves to dilute humoral elements of defense elaborated by the body. The work of Robertson, Loosli, and others demonstrates that the action of an edema-producing toxin is principally responsible for the peculiar dissemination of pneumococcal organisms which characterize lobar pneumonia. The pneumococci are swept, on a wave of edema fluid, from alveolus to alveolus through the pores of Kohn until finally further extension is halted by the interlobar barriers of serous membrane. *Fibrinolysin* may exert an effect by permitting the spread of bacteria

through what might otherwise be at least a partial physical barrier of fibrin strands. In infections with hemolytic streptococcus this may contribute to invasive properties. Coagulase activity is manifested by the ability of the bacterial organism to coagulate plasma. It is an important toxin of staphylococci and, perhaps more than any other cultural characteristic, helps to evaluate its pathogenicity. Coagulase negative staphylococci rarely cause disease. It seems paradoxical that

As a result of this specific lethal effect, the bacterial organism is indirectly protected and allowed to proliferate and/or continue to invade, since the destruction of leukocytes eliminates a major element of the body's defense against acute infectious processes. Notable examples of such action are provided by staphylococcal, streptococcal, and pneumococcal infections.

There are yet other characteristics of the bacterial cell which, although not toxins in the



MORPHOLOGIC RELATIONSHIPS OF INFECTIOUS ORGANISMS

1. *B. anthracis*, $3-8\mu \times 1-1.2\mu$.
2. *S. aureus*, $0.7\mu - 0.9\mu$.
3. *D. pneumoniae*, $.8-1.25\mu \times 1.5-2.5\mu$.
4. *H. influenzae*, $1-1.5 \times 0.3-0.4\mu$.
5. *Vaccinia virus*, 0.15μ .
6. *Yellow fever virus*, 0.018μ .
7. *Rickettsia prowazekii*, $0.3\mu \times 0.3-0.5\mu$.
8. *Tr. pallidum*, $0.2\mu \times 4-14\mu$.
9. *E. Coli*, $2-3\mu \times 1-1.2\mu$.
10. *S. pyogenes*, $0.6\mu - 1.5\mu$.

* APPROXIMATELY THREE TIMES LARGER THAN
A MOLECULE OF SERUM GLOBULIN

Fig. 129.—Morphologic relationships of infectious organisms.

Toxins which dissolve clots (fibrinolysin) and those which stimulate clot formation (coagulase) should both contribute to the effectiveness of bacterial growth and invasion. In the case of coagulase, recent evidence indicates that this toxin acts to interpose a fibrin barrier at the surface of the bacterial cell and that this inhibits phagocytosis. Leukocidin, as its name implies, is a necrotizing substance, one lethal for leukocytes.

In ordinary sense, contribute to pathogenicity, invasiveness and virulence. One of these is the capsule which is so important a part of such bacteria as the pneumococcus, meningococcus, tubercle bacillus, etc. In the case of pneumococci, the major constituent of the thick capsule is a polysaccharide. Highly virulent strains of this organism have been rendered avirulent by simply dissolving away the capsule. On the

other hand, such avirulent decapsulated pneumococci have been proved highly destructive to experimental animals with agranulocytosis. This suggests that the polysaccharide capsule serves as protection against phagocytic ingestion. In addition to this, mechanisms of humoral defense are also disturbed. Upon death of the microorganism, a considerable quantity of antigenic polysaccharide is released in soluble form. This combines with specific antibody produced by the body and effectively blocks such antibody from an effect on living pneumococci. In the case of gram-negative bacilli and cocci, organisms which do not produce potent exotoxins, the *O* (*somatic*) substances play an important part in virulence. These are quite different from the exotoxins which we have discussed since they are constituents of the bacterial cell rather than metabolic by-products. These phospholipid-protein-polysaccharide complexes constitute 5 to 20 per cent of the bacterial cell and are highly toxic as well as antigenic. They interfere with phagocytosis and also inhibit bactericidal powers of serum against the homologous organism.

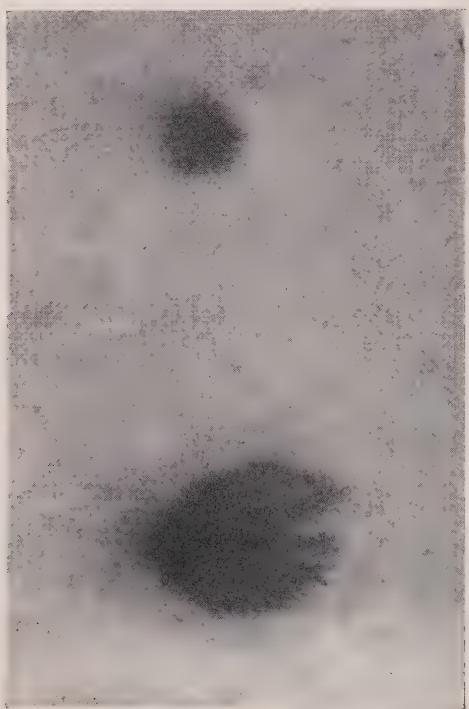


Fig. 130.—The effect of hyaluronidase upon the spread of particulate carbon (India ink) of a size comparable to staphylococci. This photograph was taken thirty minutes after intradermal injections of 0.1 c.c. of carbon suspension into rabbit. The larger lesion represents the increased spread of India ink because of added hyaluronidase.

4. Bacterial infection results in the formation of specific antibodies which may alter the "normal" inflammatory response and, in some instances, produce a superimposed allergic inflammation.

Bacterial Specificity

The problem of bacterial specificity refers to the fact that various bacteria produce specific diseases which are quite characteristic and which differ from diseases produced by other bacteria. This is only relative, in that some microorganisms produce a wide variety of lesions. For instance, *Staphylococcus aureus* may produce a furuncle (boil) or the more widely disseminated pyogenic dermal lesion, impetigo. On the other hand, this same organism may cause a particularly virulent type of acute pneumonia in infants, or a very chronic osteomyelitis. In contrast to these localized lesions, such disseminated infection as septicemia or pyemia may result. Yet, such diseases as scarlet fever, lobar pneumonia, typhoid fever, and plague are not likely to be confused with each other and each has its own distinct and separate etiology. What is the basis for these peculiarly characteristic reactions? To begin with, bacterial habitat is important in influencing the portal of entry, and hence the initial localization. In the peritonitis which invariably follows perforative appendicitis or diverticulitis, the mixed bacterial flora responsible are normal inhabitants of the intestinal tract. The fact that virulent staphylococci inhabit the skin of many apparently normal persons explains why most skin infections are staphylococcal. The initial localization does not necessarily persist, however, nor does it always influence the ultimate localization of the disease. Although the meningococcus usually enters through the upper respiratory tract, its major manifestation is most often meningitis, or perhaps a fulminating septicemia.

Many additional factors are concerned with bacterial specificity. A large proportion of these are little understood. One important factor in this preferential selection is the chemical composition and cellular metabolism, including oxygen tension, of the various tissues of the host.

Type of Tissue Related to Bacterial Infection

INFECTION OF INTERSTITIAL TISSUES

Anatomic structure has an important influence on distribution and form of local infection. For present purposes interstitial tissues may be considered to be of three major types: (a) The loose areolar tissues that offer little in the way of any mechanical barrier to limit the spread of infection—subcutaneous tissues in general, the mediastinal and periorbital tissue. It is in these tissues that cellulitis, a diffusely spreading infection, occurs. (b) Comparatively dense tissues which often contain, in addition, bands of yet denser tissue (fascia) that serve as relatively impermeable barriers and limit the extent of infection. Skeletal muscle and bone are examples of this type. (c) Tissues which include a system of preformed spaces within them—spaces which bacteria may utilize for purposes of dissemination. Common examples of this third type are the kidney, prostate, seminal vesicles, and salivary glands. In ascending pyelonephritis for instance, the passageway which extends from the external urinary meatus to the renal calyces, and thence through many elaborate

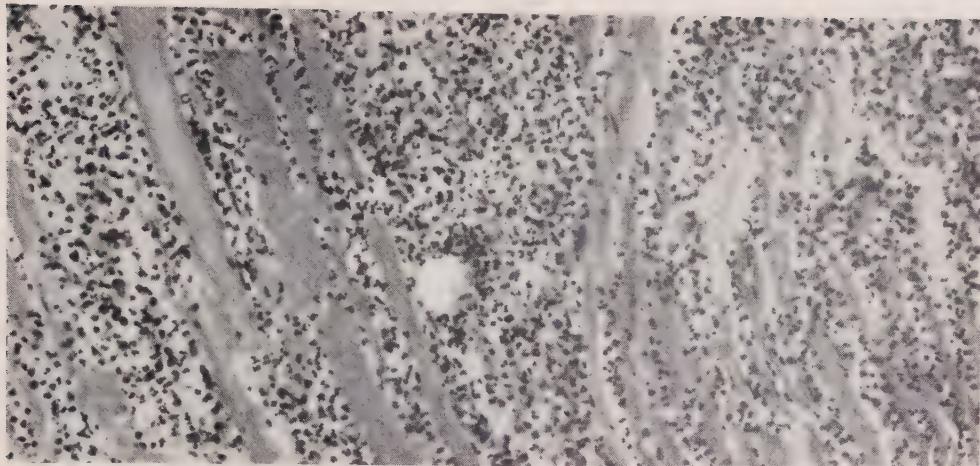


Fig. 131.—Acute myositis spread of infection along muscle fibers. Infection of an amputation stump.

tubular systems almost to the capsule of the kidney, provides a ready explanation for the ascending urinary infections which may lead to extensive diffuse pyelonephritis and ultimately conclude in uremia and death. Conversely, an isolated infectious focus (blood-borne) may develop in the renal cortex and extend, in the opposite direction, through these same preformed spaces to cause diffuse pyelonephritis of *descending* type. The skin is also an example of this type tissue since infection commonly occurs in sweat glands, sebaceous glands, and hair follicles. Occasionally, vascular channels are utilized in a similar manner. For example, in pylethrombophlebitis a septic thrombus (or thrombo-embolic portions) extends along the portal venous channels, finally reaching the liver. Here the infection is disseminated along multiple branches of the portal vein within the liver, to produce multiple abscesses throughout this organ, each in relation to a venous channel.

INFECTION OF SEROUS SURFACES

Those thin layers of loose connective tissue which are covered on their free surface by a layer of mesothelium are unique in that they always line a closed body cavity. Thus, any infection of serous membranes is, in a sense, an infection of a body cavity. In general, two special effects may result: (1) If the cavity is large and the serous surfaces present a great area for the absorption of bacterial products (e.g., peritoneal cavity), there will result toxemia. (2) If the cavity is small and its walls heavily reinforced (e.g., joint, meningeal cavity), the accumulation of exudate may cause a marked increase in pressure with tissue destruction as a result of this mechanical effect.

INFECTIONS OF MUCOUS MEMBRANES

The skin is considerably more resistant to bacterial invasion than are mucous membranes and, furthermore, mucous membranes have a much greater absorptive capacity for toxins.

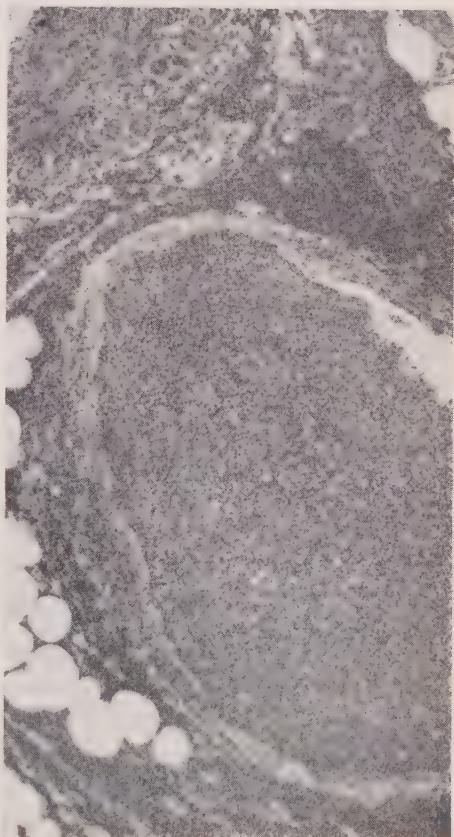


Fig. 132.—Spread of infection within vascular channels—phlebitis.

Many bacterial diseases begin in and are originally confined to mucous membranes, especially those which line the upper respiratory tract. Complications of such infections are



Fig. 133.—Healed diffuse peritonitis. This cut section illustrates the extensive fibrous adhesions and complete obliteration of the peritoneal cavity.

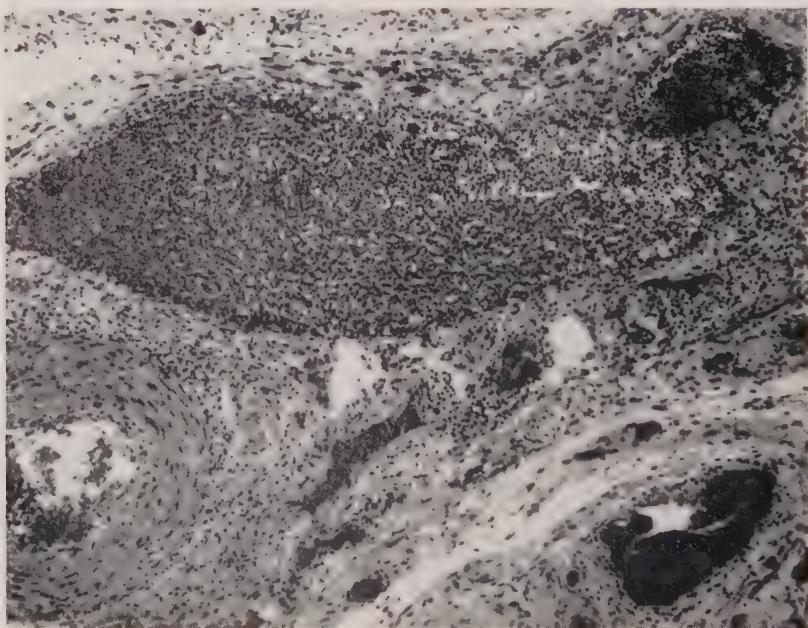


Fig. 134.—Spread of infection within vascular channels—lymphangitis.



Fig. 135.—Spread of infection within vascular channels—arteritis. An early stage of abscess formation in the liver secondary to a septic embolus which lodged within a branch of the hepatic artery. This was an effect of staphylococcal pyemia.

numerous and often quite serious. Consider, for example, some of the complications of pharyngitis—septicemia, subacute bacterial endocarditis, otitis media, thrombophlebitis of the sigmoid or cavernous sinuses with meningitis and brain abscess, pneumonia, rheumatic fever, glomerulonephritis. One special characteristic of infections of mucous membranes depends upon the ability of these epithelial cells to secrete mucus. As a result of this, in mild infections, or in the early stages of a more severe reaction, the exudate is frequently catarrhal or mucinous. If considerable fibrin is included in the exudate, it may assume the form of membrane, actually a *pseudomembrane*. If there is destruction of the underlying epithelium, the fibrin network may become quite firmly attached, as occurs in diphtheria.

TOXEMIA, SEPTICEMIA, PYEMIA, BACTERIEMIA, SAPREMIA

Toxemia.—Toxemia is that condition in which signs and symptoms are an effect of circulating toxins and not dependent upon the presence of infectious organisms circulating in the blood. Malaise, increased fatigability, and generalized aching are prominent symptoms. If neurotoxins are concerned, as in the case of botulism or tetanus, there may be paralysis of various muscles. Toxemia is usually associated with actual infection by the toxin-forming organisms, e.g., diphtheria, or gas gangrene, but this is not always so. For example, the toxins elaborated by *Clostridium botulinum* or certain staphylococci may be ingested directly to cause a very profound toxemia without true infection by the organisms responsible.

Septicemia.—In general, the whole effectiveness of the inflammatory reaction rests upon the



Fig. 136.—Acute myocardial abscess (papillary muscle). The relatively slight fibrous tissue response is compatible with its duration of but a few days (pyemia).

rapidity with which localization and destruction of the inflammant are accomplished. In this sense, septicemia represents a failure on the part of the body's inflammatory reaction because septicemia is a diffuse infection, one in which infectious organisms and their toxins are present in the blood stream. It is possible for septicemia to arise directly from the introduction of infectious organisms into the blood stream. As a rule, however, septicemia is secondary to a focus of infection within the body. In this case there are three major routes by which the organisms may reach the blood stream: (1) by direct extension and entrance into an open vessel; (2) secondary to thrombosis of a blood vessel in the area of inflammation with bacterial invasion and subsequent release of infected (mycotic) emboli; (3) following infection of lymphatic channels (lymphangitis) with extension to and infection of the lymph nodes themselves (lymphadenitis) and finally discharge of infected lymph into the blood stream via the thoracic duct or right lymphatic duct.

Many specific diseases, e.g., typhoid fever, brucellosis, etc., include a septicemic phase. In the absence of such systemic disease, beta hemolytic streptococci are most frequently responsible for septicemia. Septicemia caused by alpha streptococci (*Streptococcus viridans*) is usually a consequence of subacute bacterial endocarditis. The majority of bacteria which produce suppurative lesions may, on occasion, give rise to secondary septicemia.

Pathologic changes which characterize septicemia vary considerably, depending upon the duration and the bacterial agent which is responsible. Effects may be considered under three major headings:

DEGENERATIVE CHANGES.—These result from the action of bacterial toxins. There is marked parenchymatous degeneration of most tissues, especially evident in the heart, liver, and kidneys—there is often fatty change here too. Frequently, skeletal muscle exhibits waxy or hyaline degeneration. Areas of focal necrosis are frequently seen, especially in the liver, spleen, and lymph nodes. The thymus, particularly in children, exhibits marked atrophy. Examination of such highly specialized tissues as the testicle reveals pronounced degenerative changes. Injury to capillaries is frequently reflected by multiple petechial hemorrhages in the skin, mucous and serous membranes. There may be extensive hemorrhage within the suprarenal glands, most often as a result of fulminating meningococcemia. Often there is slight generalized edema. Microscopically, hyaline thrombi may be seen in the capillaries of many organs. Hemolysis occurs and may be evident clinically as slight icterus. At autopsy, its effects will be observed in the pink staining of the endocardium and intima of larger vessels. This is one explanation for the sudden anemia which often develops in septicemia. Another explanation is found in the bone marrow where there is toxic depression of erythropoiesis. The blood is dark and clots slowly.

DEFENSIVE REACTION.—In any serious infection save those which occur in markedly debilitated individuals, especially the very young and the

very old, certain "defensive" reactions on the part of the body will be evident. Clinically, these are manifest by fever, tachycardia, and leukocytosis. The pathologic changes which characterize this reaction of defense are especially evident in reticulo-endothelial tissues as hyperplasia of the spleen, lymph nodes, and reticulo-endothelial elements of the bone marrow and liver. The degree of change depends upon the duration and severity of the infection. Usually the spleen is enlarged several times, is hyperemic, soft, and mushy (diffused). Its pulp can be readily scraped free from the fibrous stroma. When splenic enlargement is so marked that it is readily evident upon physical examination it is often termed acute splenic tumor. A better term is acute septic splenitis or septic hyperplasia. Microscopically, sinuses are engorged with blood and contain many polymorphonuclear leukocytes. Usually the reticular elements are markedly hyperplastic. Malpighian corpuscles are large and their borders ill defined; they contain large reaction centers in which lymphorrhesis is evident. Lymph nodes are also increased in size as a result of hyperplasia and their sinuses may contain polymorphonuclear leukocytes (lymphadenitis) as well as macrophages. Occasionally, in overwhelming infections, lymph follicles may be depleted and consist largely of pale mononuclear cells rather sparsely distributed and comprising the so-called depletion centers. Reticular elements of the bone marrow and liver are hyperplastic and in the bone marrow there is usually a marked increase in immature cells of the leukocytic series, i.e., a "shift to the left." Most tissues are hyperemic and increased numbers of leukocytes are seen in blood vessels, morphologic evidence of leukocytosis.

LOCAL EFFECTS OF BACTERIA.—Foci of acute inflammation, perhaps abscess formation, may occur in almost any tissue. Depending upon the tissue involved, this may be manifest as meningitis, peritonitis, etc. Acute bacterial vegetative endocarditis is a frequent complication of septicemia.

The importance of fulminating septicemia as a cause of sudden death in individuals who were apparently well a few hours or a day before has been realized but recently. Approximately 15 per cent of sudden, unexpected deaths in military personnel (1942 to 1946) were found to be from this cause.

Pyemia.—Pyemia, or septicopyemia, is that condition in which pyogenic organisms (and their toxins), notably *Staphylococcus aureus*, are carried in the blood stream and initiate multiple abscessive foci. Many of these circulating organisms are in the form of agglutinated clumps and are of sufficient size to cause embolic phenomena. The characteristic areas of focal suppuration, many of which are actually septic infarcts, are thus explained. Each new abscess may, in turn, contribute additional septic emboli. At autopsy the striking feature is the multiplicity of abscesses involving many tissues. Before the advent of sulfonamides, penicillin, etc., staphylococcal pyemia carried a mortality of approximately 90 per cent.

Bacteriemia.—Septicemia is to be sharply differentiated from bacteriemia in which, al-

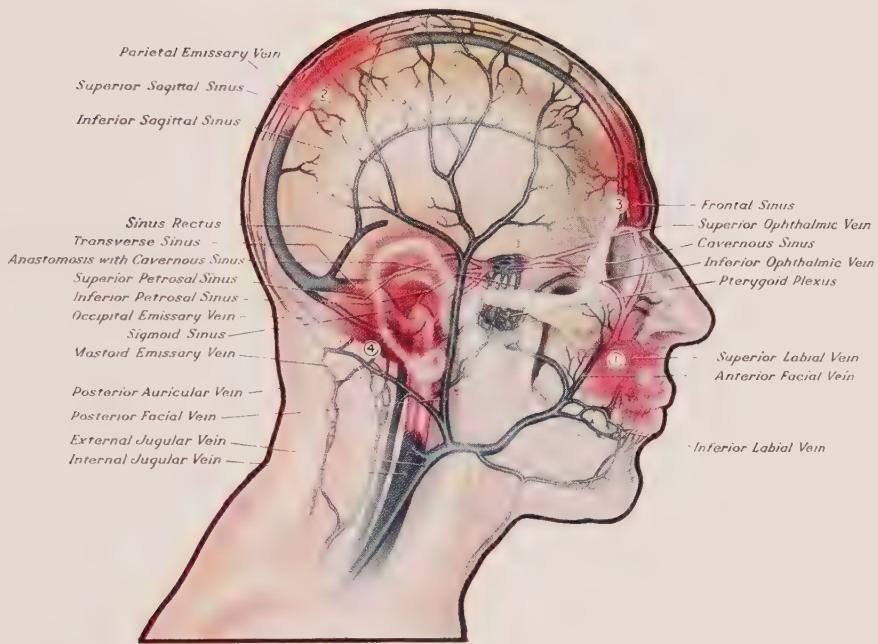


PLATE I.—Spread of infection within the head along venous channels.

1, *Furuncle of the upper lip*: Spread of infection by way of the superior labial, anterior facial, and ophthalmic veins leading to septic cavernous sinus thrombosis.

2, *Infected wound of the scalp*: Spread of infection by way of emissary veins to the superior sagittal sinus and from there to cerebral veins (retrograde) causing brain abscess.

3, *Frontal sinusitis*: Spread of infection by way of small veins which drain directly into the superior sagittal sinus. From here infection may extend to cerebral veins causing brain abscess or by way of the superior ophthalmic vein to the cavernous sinus causing septic thrombosis of this sinus.

4, *Otitis media and mastoiditis*: Spread of infection to sigmoid sinus and, by way of petrosal sinuses, to the cavernous sinus to cause septic thrombosis. Extension of infection to adjacent brain tissue may also occur, either by contiguity or through small venous channels, leading to brain abscess.

A major complication in all these instances is widespread dissemination of the infection, since septic thrombosis of intracranial venous sinuses may extend into the internal jugular vein, resulting in septicemia.

though bacteria may circulate in the blood stream, there is no associated toxemia, nor are there clinical manifestations. Bacteriemia is usually transient and may last only a few moments. Under favorable conditions, the reticulo-endothelial system localizes and destroys these organisms. It is estimated that a normal individual experiences bacteriemia, unknowingly, many times each year. Certainly this state almost invariably follows the extraction of teeth for apical abscess, major traumatic wounds, etc. Bacteriemia is of great importance since it provides the means by which many apparently isolated infections of internal organs arise, e.g., osteomyelitis, cholecystitis, pyelonephritis (descending type), or subacute bacterial endocarditis.

Sapremia.—Sapremia may be defined as the presence in the blood stream of poisonous metabolites resulting from the growth of saprophytic organisms in necrotic tissue. This is most commonly encountered in certain types of gangrene.

INFECTIONS BY SPECIFIC BACTERIA

Staphylococcal Infection

Common diseases and lesions which result from staphylococcal infection are: furuncle, carbuncle, impetigo, acne, paronychia, felon, abscess, phlegmon, osteomyelitis, arthritis, tonsillitis, sinusitis, otitis media, bronchitis and bronchopneumonia, septicemia, and pyemia. *Staphylococcus aureus*, a gram-positive coccus, unencapsulated and nonspore-forming, which grows in grapelike clusters, is the most common cause of suppuration, i.e., pyogenic infection. It is frequently associated with other pathogenic organisms as a contributor to mixed infections. The presence of these organisms can add materially to the chronicity of such diseases as pneumonia, diphtheria, and scarlet fever. Staphylococci are the common cause of purulent infections of the skin and subcutaneous tissue and may play a major role in wound infection. As they are frequently responsible for otitis media and sinusitis, so may they cause meningitis and brain abscess. In the majority of instances they can be obtained in pure culture from lesions of osteomyelitis. They are the most common cause of pyemia and may result in acute vegetative endocarditis. In infants and children, staphylococcal bronchopneumonia carries a relatively high rate of mortality. Particularly in pyelonephritis of hematogenous origin, staphylococcus is often the causative agent.

Clinical types of staphylococcal infection include the following: *Impetigo contagiosa* is an infectious and communicable disease largely restricted to children. It is caused most often by staphylococci and involves the superficial layers of the skin resulting in the formation of pustules, vesicles, crusts, or bullae. In the newborn or in debilitated infants it occasionally results in death. Less often, the disease is caused by streptococci when it is more severe and carries an additional hazard in that glomerulonephritis may be an ultimate consequence. In the adult, the most common dermal or subcutaneous focus of suppuration is the *furuncle* (boil). This is a typical abscess and, as such, has been described (page 43). Multiple furuncles (furunculosis) may form in a particular area such as the axillae or back of the neck. This localization is related to the regional concentration of sebaceous and sweat glands and hair follicles, influenced too by susceptibility of these areas to mechanical trauma or chemical irritation from the use of depilatories or antiperspirants. The *carbuncle* is a complex, focal, suppurative lesion which results when the infectious process, similar to that of a furuncle, extends laterally through the dense bands of fibrous tissue contained in the deep adipose tissue. New foci of eruption occur in relation to vertical strands of fibrous tissue so that an extensive cluster of "furuncles" presents—each connected with the other in the deep tissues. This most commonly occurs in the neck, for there the subcutaneous tissue is thick and contains much dense fibrous tissue. The severity of the type of infection and its chronicity are understandable when one considers the number, complexity, and relative inaccessibility of the deep suppurative pockets.

Paronychia and *felon* are focal suppurative lesions in which, again, special characteristics are an effect of anatomic structure. In paronychia, the infection extends around the side and base of the fingernail resulting in a very painful and rather disabling lesion. It may lead to the loss of the nail. Mechanical injury, often a hangnail, usually provides the portal of entry. Felon is a deep-seated infection which occurs in the anterior portion of the distal phalanx of the finger, usually secondary to a penetrating wound. Since this region is essentially a closed space, surrounded by a dense fibrous membrane, the exudation (suppuration) which follows bacterial infection leads to progressively increasing pressure and intense pain. If the process is

allowed to continue, there will be compression of blood vessels, ischemia, and ultimately necrosis of bone followed by osteomyelitis. Effective local treatment obviously provides for drainage and thus decompression. In these conditions, as with all foci of bacterial infection, a major complication is spread to neighboring tissues or, most serious, a generalized infection, i.e., septicemia or pyemia.

Wound Infection.—The distinction between wound contamination and wound infection has long been made since almost all wounds are contaminated (contain bacteria), but relatively few are infected, i.e., manifest disease as a result of bacterial inflammation. Bacterial infection of a traumatic wound carries a double hazard. First, the infection itself may result in toxemia, or extend to produce extensive tissue damage and

wounds. In the case of *Staphylococcus aureus*, the observed carrier rate for adults is about 50 per cent. Wound contamination by this organism is more common among those who carry it on their skin, and usually the organism found in the wound is of the same serologic type as that found on the skin. Beta hemolytic streptococci are present in the throat of 5 to 15 per cent of healthy persons. These organisms are found on the skin infrequently and in but small numbers, even in carriers. As might be suspected from this, infection with this organism is uncommon in fresh wounds. In older wounds and those in which considerable tissue destruction has occurred, infection by hemolytic streptococci is a frequent and serious complication. It appears that much of this is not related to initial contamination, but represents added infection. An



Fig. 137.—Impetigo. Older lesions are dark and encrusted. (From Top, Communicable Diseases, The C. V. Mosby Co.)

perhaps septicemia. Second, local infection delays healing of the wound and may be a basis for serious hemorrhage or disruption. Bacterial organisms most commonly responsible for wound infection are *Staphylococcus aureus*, beta hemolytic streptococci, and gram-negative intestinal bacilli—in this order of frequency. The type of microorganisms found tends to vary with the area involved. Large wounds of the trunk, buttocks, and thighs are particularly susceptible to heavy infection with coliform bacilli as a result of the almost constant contamination of this area by fecal organisms. It is pertinent here to consider the carrier rate and local distribution of organisms which commonly infect

important part of the treatment of wounds is prophylactic and the general practice of débridement, whenever extensively traumatized or ragged tissue presents, is most important to minimize the hazard of infection. Antibiotics and sulfonamides have greatly reduced the incidence of wound infection.

Streptococcic Infections

We are primarily concerned here with those gram-positive cocci, growing in chains, which produce alpha or beta type hemolysis when cultured on blood agar.



Fig. 138.—Inception of a carbuncle. Observe the multiple streaklike abscesses extending along hair follicles up toward the epidermis. These would soon have pointed in multiple foci so as to form a cluster of abscesses.

Alpha hemolysis is characterized by greenish discoloration and partial hemolysis of the blood corpuscles immediately surrounding the colony. Because of this reaction this organism, *Streptococcus viridans*, is often called green, alpha, or nonhemolytic streptococcus. In *beta* hemolysis, the colonies are surrounded by a sharply defined area in which erythrocytes are completely hemolyzed and colorless. This type of hemolysis characterizes so-called hemolytic streptococci. These *beta* hemolytic streptococci are more virulent and have a much greater capacity for invasion than do *alpha* streptococci. A third type, termed indifferent streptococci

(gamma type), of little significance in the production of human disease, causes no hemolysis at all.

In addition to a purely local effect observed on blood agar media, beta hemolytic streptococci (when grown in a culture medium that contains serum) produce a soluble hemolytic toxin, streptolysin, that will produce death when injected into susceptible animals. Such animals exhibit hemoglobinuria and give other evidence of intravascular hemolysis. Clinically, serologic studies to determine the serum titer of anti-streptolysin are of value in diagnosis and prognosis of rheumatic fever and glomerulonephritis. Largely upon the basis of Lancefield's work, beta hemolytic streptococci have been divided into a number of different groups, dependent upon the occurrence of different serologically active polysaccharides. The majority of these hemolytic streptococci which are pathogenic for man fall into group A, although occasionally strains from groups B, C, D, or G may cause infection. Group B strains have been recovered largely from cases of mastitis in cattle; group C streptococci, from a variety of lesions in



Fig. 139.—Perirenal abscess. Observe that the infection is extending into the renal cortex. Such a process may lead to pyelonephritis of the descending type.

horses, cattle, and other animals; group D occurs principally in cheese and in feces; it includes the enterococci. Group A, *Streptococcus pyogenes*, which is of most importance in human disease, has been further divided into numbered types on the basis of agglutination tests. As yet these numbered types do not appear to correlate with specific streptococcal diseases.

In contrast to staphylococccic lesions, where suppuration is characteristic, streptococccic infections are often nonsuppurative. This is by no means a rule, however; marked diversity of reaction is an outstanding characteristic of streptococccic infection. Examples of focal

mechanism although much remains yet to be explained. The high frequency of streptococccic infection is due not only to the pathogenicity of this organism, but also to its wide distribution in nature. *Str. pyogenes* is found in the throat of 8 to 10 per cent of the normal adult population. Occurrence of this organism in the nose is a much more serious matter. Hamburger and associates and Robertson have demonstrated that nasal carriers scatter very large numbers of these organisms in the air and are also much more likely to infect their hands, clothing, etc., than are oral carriers. *Str. viridans* is



Fig. 140.—Droplet infection. Droplets expelled by a violent unstifled sneeze, just completed. An intense flash of light, 1/30,000 of a second in duration, provides illumination and "stops" the course of these droplets so far as the camera is concerned. (Courtesy Dr. Harry E. Morton and the Society of American Bacteriologists).

lesions include otitis media, appendicitis, impetigo, wound infections, tonsillitis, and pharyngitis. More generalized diseases are puerperal sepsis, bronchopneumonia, meningitis, erysipelas, scarlet fever, and septicemia. In addition to these, streptococccic infection is undoubtedly concerned with, although not the immediate cause of, rheumatic fever and glomerulonephritis. It appears that allergic reaction to the products of bacterial growth, or the infectious process, is the direct causative

found almost invariably in the nasopharynx of normal individuals and is a normal inhabitant of the small intestine.

Streptococccic infections of the tonsils, lungs, appendix, etc., may be closely simulated by infections with other organisms. Certain diseases such as scarlet fever and erysipelas, however, are produced only by streptococci. Focal streptococccic infections, although occasionally suppurative, more characteristically produce a serous or serosanguineous exudate. They tend also to be less well circumscribed than the conventional staphylococccic lesion. This resistance

to localization is, in part at least, an expression of the various exotoxins produced. Characteristically, again in contrast to staphylococcal infections, the lesion is associated with painful enlargement of regional lymph nodes (lymphadenitis). There is also usually fever, malaise, and other general manifestations of toxemia.

Sore throat, when of infectious etiology, is more properly termed nasopharyngitis. Beta hemolytic streptococci (*Str. pyogenes*) is one of the most frequent and certainly the most important cause. As a rule the infection is superficial and is characterized by a swollen velvety red pharyngeal mucosa with swollen tonsils the crypts of which exude purulent exudate. In addition to local pain, swelling, and tenderness, generalized discomfort, headache, and malaise usually provide clinical evidence of toxemia. The process may extend further. Local extension may produce peritonsillar abscess (quinsy). With suppuration of or around the tonsil there may be such swelling as to cause marked mechanical interference with eating and breathing. As a consequence of peritonsillar abscess, there may be wide dissemination of the infection through the soft tissues of the neck resulting in cellulitis, i.e., Ludwig's angina. Before the advent of chemotherapy and antibiotics such a complication caused death in the majority of cases. Extensive regional extension may come about in another way, the result of suppuration within cervical lymph nodes with spread along fascial planes to cause retropharyngeal or lateral pharyngeal abscess. Extension may occur to tissues of other regions as well, and both otitis media and sinusitis are frequent complications of streptococcal pharyngitis. Epidemic forms of streptococcal nasopharyngitis have occurred as a result of ingesting milk contaminated with *Str. pyogenes*. In such cases, the source of infection may be traced either directly or indirectly to human beings. In the latter case, the cow contracts streptococcal mastitis (group A) in an unnatural manner, as a result of contact with a dairy worker infected with or a carrier of this organism. Septicemia is a complication especially feared. Finally, in considering complications of streptococcal nasopharyngitis and tonsillitis, too much emphasis can hardly be placed upon the relationship which these infections bear to rheumatic fever and glomerulonephritis.

Bronchopneumonia of streptococcal etiology is most likely to occur as a secondary infection, particularly following such virus diseases as measles or influenza. In the great influenza epidemic which occurred during World War I, the majority of deaths was actually the result of streptococcal pneumonia. In these cases tracheitis and bronchitis were striking features. The pneumonia was largely interstitial, tending to involve mostly those regions around bronchioles and this was manifest grossly by small white areas of nodular induration. Alveolar exudate was predominantly serous as a rule.

Erysipelas, a specific form of cellulitis caused by beta hemolytic streptococcus, illustrates the diffusely spreading nature of many streptococcal infections. It usually begins without

obvious portal of entry although occasionally a primary injury or defect can be demonstrated. The lesion is most often self-limited except in the very young or very old. The tissue involved is the subcutaneous tissue, usually of the face, but occasionally of the trunk or extremities. There is marked interstitial edema of subcutaneous tissues and this exudate contains fibrin, some extravasated erythrocytes, and moderate numbers of inflammatory cells, mostly monocytes and lymphocytes. Streptococcal organisms are present in great quantities in this fluid, especially in the zone of subepidermal tissue just in advance of the spreading lesion.



Fig. 141.—Spread of infection along preformed spaces, air passages—bronchopneumonia. Observe the bronchiole which is almost filled with cellular exudate—note that a portion of its wall has been destroyed and that the exudate is "spilling" into the alveoli.

In spite of this, there is little evidence of necrosis. Suppuration does not occur except as a complication. The marked reddish discoloration which characterizes the lesion and from which the name erysipelas is derived is an effect of marked congestion. Direct injury to blood vessels is evident also in the hemorrhage which occurs per diapedesis. It is by this means that erythrocytes are contributed to the exudate and blood pigment accumulates within macrophages. Usually within a week or ten days there is spontaneous remission and shortly thereafter complete healing occurs. Clinically, although the sharply circumscribed brawny



Fig. 142.—Cellulitis—erysipelas. The cells of inflammation are extending through the loose, edematous, hyperemic, subcutaneous tissue.



Fig. 143.—Facial erysipelas. Note sharp demarcation of the discolored edematous area. (From Top, Communicable Diseases, The C. V. Mosby Co.)

edematous area, discolored a fiery red, is dramatic, the outstanding feature is profound toxemia. (See Fig. 143.)

Scarlet Fever (Scarlatina).—The precise etiology and pathogenesis of this disease was not evident until the Dicks (1924) demonstrated that an erythrogenic toxin, obtained from broth filtrate of certain beta hemolytic streptococci would, upon injection into a susceptible individual, produce a typical erythematous reaction. As a result of widespread application of the Dick test, it became apparent that only a minority of adults were susceptible to scarlet fever and that the number who were "immune" was far in excess of those who had actually had the disease previously. Thus some of the difficulties in earlier experiments were explained. It appears that repeated experiences with *Str. pyogenes* may confer immunity to scarlet fever even though the disease per se has not been experienced. Further evidence of the significance of erythrogenic toxin in production of scarlet fever is furnished by the Schultz-Charlton phenomenon, and this is used also as a diagnostic test. When a patient with scarlet fever is given an intradermal injection of a small amount of specific antiserum (convalescent serum), there occurs rather promptly, in the immediate area, a blanching of the characteristic erythematous rash. Since the specific effect of such an injection is neutralization of the streptococcal toxin, it follows that the generalized skin reaction must be an effect of toxemia. The importance of individual variation in the host is illustrated by the fact that several or all members of a family may develop streptococcal pharyngitis from the same strain of organism, yet only one of the group may develop scarlet fever, the others manifesting only nasopharyngitis. It is apparent from this that scarlet fever may be contracted from an individual who has only streptococcal pharyngitis.

In the early stages there is a rather severe pharyngitis and tonsillitis. This, together with fever, vomiting, and headache make up the four cardinal prodromal symptoms of scarlet fever. Because there is no specific strain of beta hemolytic streptococci responsible for scarlet fever, bacteriologic studies do not provide a means for early diagnosis, i.e., a diagnosis of throat infection caused by *Str. pyogenes* is not a diagnosis of scarlet fever. The diagnosis cannot be positively made until the second stage of the disease is reached, one to five days after the onset. This is characterized by erythematous rash and it is this skin reaction, more than any other feature, which defines scarlet fever as a distinct disease entity. The marked hypervolemia and resultant red coloration of the skin is a manifestation of toxic injury (atony and dilatation) of vascular endothelium. This hyperemia blanches upon pressure and disappears upon death so that little of the characteristic skin reaction is ever evident at autopsy. There is edema of the skin and, particularly around hair follicles, there are focal aggregations of lymphocytes and monocytes. Within the epidermis itself, in the middle layers, there accumulates inflammatory exudate and an accelerated keratinization at this level, pseudo-

keratosis. It is because of this that desquamation occurs sometime between the fifth to twenty-fifth day; the outer layers of skin separate from the intermediate zone which has become keratinized. The tongue usually participates in this reaction too. During the first few days it presents a "strawberry" appearance because of the erythematous papillae which project from a gray-coated background. When "peeling" occurs, it becomes beefy red and glistening. Complications are divisible into three major categories: (1) an effect of bacterial dissemination locally—otitis media, sinusitis, cervical adenitis, acute suppurative mastoiditis and retropharyngeal abscess; (2) the result of bacterial dissemination generally—metastatic foci of infection throughout the body, or frank septicemia; (3) a manifestation of extraordinary reactions to toxins, and this may be brought about by hypersensitivity—interstitial nephritis or myocarditis, pericarditis, nonsuppurative arthritis, and glomerulonephritis.

Puerperal Sepsis.—In the days before anti-septic surgery, this disease was a most important cause of death. In the maternity hospitals of that day, as many as one woman out of six who entered died of septicemia. The very efforts which were exerted to determine the cause of this dread "childbed fever" served only to spread the disease, since the careful dissection and study of these dead women, by their accoucheurs, made gross contamination a certainty and this increased the likelihood that the next patient would be infected too. Semmelweis, through his painstaking studies, and Oliver Wendell Holmes, by his brilliant writings, convinced the physicians and midwives of that day that childbed fever was the result of infection and that the etiological agent was one introduced by "unclean hands." Today, many of the cases of puerperal sepsis follow criminal abortions performed by unskilled and unclean persons.

The inevitable trauma incident to separation of the placenta from its site of implantation and from passage of the fetus through the cervical os and birth canal provides opportunities for bacterial invasion comparable to that offered by an open wound. *Str. pyogenes* is the organism responsible for most cases of puerperal sepsis. Since there is very low "natural" incidence of *Str. pyogenes* in the vaginal flora during or immediately after the puerperium it follows that infection is usually extrinsic in origin. Colebrook and Hare reviewed sixty-three cases of puerperal sepsis in which approximately one-third were shown to be the result of infection by *Str. pyogenes*, antigenically identical with those obtained from the patient's throat or nose; in slightly over one-half of the cases, hemolytic streptococci of identical strain were isolated from the nose or throat of the doctor in attendance or from other persons who had been in close contact with the patient. Anaerobic streptococci, especially following abortion, may also be causative.

Clinical signs of puerperal endometritis usually make their onset three or four days after labor, but may be delayed for as long as two or three weeks. Symptoms are predominately those of

septicemia and include a septic type fever, often with chills. Infection of the uterus as such does not ordinarily cause much discomfort although this organ may be somewhat enlarged and tender to palpation. The vaginal discharge (lochia) may be either scanty or abundant but is usually of foul odor. Within the uterus the inflammatory process is rather superficial and tends to be unimpressive. Thrombophlebitis is the really significant local change since this is the means by which wide dissemination of the infection is accomplished. Uterine, pelvic, and ovarian veins may all be involved. Septic thrombosis of the femoral vein may also

ously. Most often this is caused by *Str. pyogenes*, but it also commonly results from pneumococci, staphylococci, gonococci, and influenza bacilli. Any organism which can cause septicemia may produce acute bacterial endocarditis. Subacute bacterial endocarditis (endocarditis lenta) is much more important since endocarditis in this instance represents the primary lesion and is a cause of blood stream infection rather than a result. *Str. viridans* is the organism responsible in approximately 95 per cent of the cases and *H. influenzae* in approximately 3 per cent. Infection of the heart valves is secondary to bacteremia. Usually the cause of this bacteremia is not apparent. Often, however, it is a direct result of tooth extraction. Normal heart valves are practically never subject to the type of "chronic" infection which characterizes subacute bacterial endocarditis. Previous injury by rheumatic fever is by far the most common predisposing cause, although such congenital anomalies as bicuspid aortic valve, septal defects, and patent ductus arteriosus also predispose. See page 465.

"Focal Infection."—In addition to the possible hazard of local spread or wide dissemination it has been postulated that focal infections, especially those produced by *Str. viridans*, may in some rather mysterious manner be responsible for a variety of complaints such as rheumatic fever, rheumatoid arthritis, sciatica, myositis, neuralgia, etc. Benjamin Rush probably gave stimulus to this concept by his report in 1801 of the cure of a patient with rheumatism of the hip following extraction of a tooth. Foci of infection most often considered responsible for such diseases are: apical infections of the teeth, gingivitis, tonsillitis and, less often, cervicitis, prostatitis, or cholecystitis. It is the general opinion today that more harm than good has resulted from the indiscriminate extraction of teeth, tonsils, etc., in treating the diseases mentioned above. The mechanism by which focal infection leads to such systemic conditions as rheumatic fever or rheumatoid arthritis is not clearly defined by those who claim this to be the etiology. A peculiar reaction to bacterial toxins, possibly as a result of hypersensitivity, has been considered.

Pneumococcal Infections

Diplococcus pneumoniae is responsible for most cases of lobar pneumonia and many cases of bronchopneumonia. Since its portal of entry is the respiratory tract, it is quite understandable that pneumococci are often responsible for otitis media and paranasal sinusitis. Brain abscess may follow as a result of septic thrombosis of venous sinuses of the brain. Pneumococcal meningitis is occasionally seen without antecedent pneumococcal infection, although most often it is secondary to an upper respiratory process. Its manifestations are similar to those of other pyogenic meningitides. Suppurative arthritis, acute bacterial endocarditis, and peritonitis are complications of bacteremia or septicemia.

Diplococcus pneumoniae resembles *Str. viridans* so closely in its morphologic characteristics that the British list the pneumococcus as a member of the genus *Streptococcus*. However, the characteristic of bile solubility and special antigenic



Fig. 144.—Focus of infection. This longitudinal section of the root end of an upper anterior tooth *in situ* shows a chronic infectious process (root end granuloma) which followed the necrosis of the dental pulp. The considerable resorption of bone and replacement by soft tissue accounts for the roentgenographic appearance of a dark area surrounding the root tip. (Courtesy Dr. J. R. Blaney.)

occur. A second route by which infection often spreads is via the lymphatic channels, extending along the broad ligaments and other attachments to celiac lymphatic cistern and thence to the thoracic duct and subclavian vein. Peritonitis is a frequent accompaniment of septic endometritis.

The role of streptococci in wound infection is discussed on page 200.

Endocarditis.—*Acute endocarditis*, as a complication of septicemia, has been mentioned previ-

properties serve to differentiate this oval- or lance-shaped encapsulated gram-positive coccus. The organism usually occurs in diplo-form, but may form short chains. Serologic studies have been mostly concerned with those pneumococci isolated from cases of lobar pneumonia. It was the systematic studies of Avery, Dochez, and associates which led to the establishment of specific types I, II, and III, leaving a large residual group of unclassified types, group IV. Cooper and her associates extended these observations and separated from group IV twenty-nine additional types. Still further studies have led to the isolation of many more types. However, almost all strains of pneumococci pathogenic for man are included in types I, II, III, and Cooper's additional twenty-nine. There is an important practical aspect of this work since these serologic differences, the result of specific capsular polysaccharides, determine antigenic behavior and are responsible for the fact that antibodies produced against one type are effective only for that particular type. Before chemotherapy and antibiotics proved so effective, serum therapy was extensively used in the treatment of pneumococcal pneumonia and it was essential that the type of organism be known so that type specific antiserum could be given promptly. The determination of type is easily accomplished by mixing the organism (from sputum or the peritoneal exudate of an infected mouse) with type-specific antiserum. When the type of organism and antiserum correspond, marked swelling of the capsule becomes readily apparent (Neufeld reaction). Before the First World War, lobar pneumonia was thought to be primarily endogenous in origin since it could be demonstrated that many apparently healthy individuals carried pneumococci in their throats. It was observed, however, that frequently when lobar pneumonia developed among a large group of men closely associated together, as in a barracks, the great majority of cases were caused by organisms of the same serologic type and that this type was foreign to the person infected. Nearly all persons harbor pneumococci in their nasopharynx although from a single determination the incidence would appear to be but 40 to 50 per cent. As many as seven different types have been reported in a single carrier at one time. It is these same types that are frequently responsible for postoperative or postinfectious pneumococcal pneumonia, the result of lowered resistance. This form of infection usually results in bronchopneumonia.

The investigations of Robertson, Loosli, and co-workers leave little doubt that lobar pneumonia results from bacterial entry and invasion by the bronchial route, and that the infection spreads through the respiratory passageways rather than by hematogenous or lymphogenous means. The presence of mucin has been shown experimentally to promote invasion of the pneumococcus as well as certain other organisms. This has been variously explained as an inhibitory effect on phagocytosis or intracellular digestion, and interference with bactericidal properties of the blood. Thus aspiration of pneumococcal organisms incorporated within mucus would favor development of the disease.

This explains, in part, the fact that lobar pneumonia frequently follows a cold. For a detailed discussion of this disease see page 673.

Meningococcic Infections

Neisseria meningitidis, a small oval- or bean-shaped gram-negative coccus, usually occurs in pairs, occasionally in tetrads; it closely resembles the gonococcus morphologically. A capsule may be demonstrated, but is not usually apparent. As in the case of pneumococcus, types based on antigenic differences are of practical importance since immunity is largely type specific. Four serologic types have been described. The phenomenon of capsular swelling (Quellung reaction) occurs when the organisms are mixed with type-specific serum and is similar to that described for pneumococci. This is not of therapeutic importance today since sulfonamides have proved so effective in treatment. The two major diseases which result from infection with this organism are: meningitis and a fulminating form of septicemia.

Meningococcic meningitis (cerebrospinal fever, epidemic cerebrospinal meningitis, spotted fever) may be sporadic, endemic, or epidemic. It affects children and young adults most often. The source of infection is usually a healthy carrier or a person recently recovered from the disease. Ordinarily the population at large will include 2 to 5 per cent of healthy individuals who harbor meningococci in their nasopharynx. When this figure approaches 20 per cent there is danger of an epidemic. During the height of an epidemic, the carrier rate may reach 70 per cent. Obviously the virulence of the prevailing strain of organisms will be of equal if not greater importance than the number of carriers per se. The disease is not highly contagious and the infection rate rarely exceeds 1 per 1,000 even during epidemics. Under conditions of crowding and poor sanitation, however, as occurred in some army camps of the First World War, the attack rate may be as high as 1 per 20.

Meningococcic meningitis is conveniently considered under three stages. The portal of entry is the nasopharynx, and stage one consists of a local infection in this area. This initial reaction is rarely given significance by the patient and may escape notice. Stage two is characterized by septicemia (in approximately 25 per cent, organisms are readily demonstrable in venous blood) and symptoms do not point toward any specific organ. There is fever, often associated with slight chills. The patient complains of generalized aching and prefers to lie still and quiet. The most striking feature is the rash which has led to the term spotted fever. These "spots" begin as small areas of erythema; soon, however, hemorrhage is evident as a result of thrombosis of arterioles and capillaries. Most of these are petechial in form (less than 2 mm.) but there may be confluent areas with a diameter as large as 1 cm. Fulminant forms often present massive purpuric hemorrhages and the regions so involved may become gangrenous. At this time, should a spinal puncture be made, the fluid would appear essentially normal. Stage three is the period

of metastatic localization, principally to the cerebral meninges. Intense headache, vomiting and prostration is followed by drowsiness or irritability and later by delirium or stupor which may progress to coma. There is stiffness of the neck and, especially in children, a rigid posterior curvature of the back, opisthotonus. Another manifestation of muscular spasm prevents flexion of the knee when the leg is extended at right angles to the body, Kernig's sign. At this time examination of the spinal fluid is diagnostic. There is increased pressure, often over 300 mm. of water, and the fluid is cloudy or turbid because of its high content of leukocytes, mostly neutrophiles. Sugar is usually markedly reduced or absent altogether.

is present, most prominent over the base of the brain, filling in around vessels and sulci and often obscuring cranial nerves. The vessels of the pia are engorged. The ventricles contain no great excess of fluid, but the fluid is turbid and contains pus cells. Careful microscopic examination usually demonstrates the marked efficiency of the pia as a mechanical barrier preventing the spread of organisms into the brain substance. Degenerative changes are present in the superficial layers, however, as a result of the diffusion of toxins. The inflammatory exudate is composed principally of polymorphonuclear leukocytes and these are enmeshed in numerous strands of fibrin. Exudate is densest around blood vessels and may follow



Fig. 145.—Purpura in fulminating meningococcemia. (From Top, Communicable Diseases, The C. V. Mosby Co.)

Smears of this fluid (sediment obtained by centrifugation) frequently reveal the characteristic diplococci. The ratio between intra- and extracellular organisms is of prognostic value. Sometimes the fluid must be cultured in order to detect the presence of meningococci. Within the brain, the first changes occur in the blood vessels of the leptomeninges (pia and arachnoid) and are hyperemia, slight serous exudation, and minute areas of hemorrhage. This progresses and soon cellular exudate becomes apparent. The pathologic picture varies depending upon the age and severity of the disease. In an advanced stage, thick purulent exudate

these vessels for some distance within the substance of the brain. These morphologic changes are similar to those which occur in most types of purulent meningitis. There is often focal encephalitis evident as minute aggregations of leukocytes and perhaps tiny hemorrhages. In cases that succumb within the first few days, cerebrospinal fluid will be increased in amount, but there will be no evidence of hydrocephalus. In chronic forms, internal hydrocephalus is often striking. Prior to specific therapy, the mortality rate averaged 60 to 70 per cent. Today, the expected mortality is 5 to 10 per cent.

Meningitis may be complicated by blindness or deafness from direct involvement of cranial nerves. Strabismus and facial weakness or spasm may follow injury to cranial nerves III and VII. Otitis media is common. Other organs are not immune to metastatic infection. Endocarditis and occasionally purulent monoarthritis occur. This latter is to be differentiated from the transient polyarthritides that frequently occurs, probably as an effect of hemorrhage within the joint. Pneumonia often complicates severe forms of the disease. When this occurs there may be meningococcic infection of pulmonic tissues; however, the infection is usually of mixed type and bacteria such as staphylococci and streptococci exert the major effect.

Fulminant Meningococcemia.—In these cases, the onset of symptoms is precipitous and the disease runs a violent and rapid course. Moritz and Zamcheck in their comprehensive study of "Sudden and Unexpected Deaths of Young Soldiers" found that meningococcemia was responsible for 110 of approximately 750 sudden and unexpected deaths. This figure represented roughly one-third of the total reported deaths (Army) from meningococcus infection. More than half of these patients died within six hours after coming under medical observation. In all instances, death occurred within twenty-four hours after onset of incapacitating symptoms although approximately 70 per cent had had prodromal signs in the form of a mild upper respiratory infection or subnormal feeling. Clinically, the predominant manifestation was peripherovascular collapse and shock; cyanosis was often a prominent feature and cutaneous hemorrhages were observed in the majority. This picture is essentially similar to that seen in infants or children. Clinical evidence of meningitis is not common because the rapid course of the disease usually leads to death before opportunity for marked involvement. Even though meningeal involvement does occur, symptoms are frequently masked by the shocklike state of collapse. The term *Waterhouse-Friedrichsen syndrome* is applied to this condition when, in addition to cutaneous hemorrhages, there is hemorrhage into the adrenal gland; this is usually massive and bilateral. Some have considered the state of collapse, which is so prominent in this condition, as a manifestation of acute adrenal cortical deficiency. However, complete cessation of adrenal cortical function does not produce peripherovascular collapse within so short a time. The action of bacterial toxins seems sufficient to explain the clinical picture in the majority of cases. Black-Schaffer and associates have demonstrated that those strains of meningococci which produce considerable amounts of Shwartzman toxin are more likely to produce hemorrhage and suggest that this reaction may be related to the Shwartzman phenomenon. A presumptive diagnosis of meningococcemia should be made in any fulminating septic state, especially when accompanied by purpuric hemorrhages, so that decisive treatment can be instituted at once. The time required to secure positive blood cultures is not compatible with prompt action. Repeated examinations of blood smears may

disclose meningococci. A more reliable method is to examine smears obtained from areas of petechial or purpuric hemorrhage.

Gonococcic Infections

Neisseria gonorrhoeae is the other important member of the group *Neisseria* and was the first member of this group to be described. Its detection in inflammatory exudate from gonorrhreal lesions by Neisser, in 1879, settled the long controversy as to the true nature of this disease. The organism is very similar to the meningococcus. It is gram negative and most often occurs in diplo-form. There has been some question as to the character of toxins produced by this organism, but toxic action, in experimental animals, seems largely, if not entirely, a result of endotoxins, as is also the case with the meningococcus. Studies of serologic types have yielded very irregular results. The organism is fastidious in its growth requirements and quickly dies under unfavorable conditions so that infection (except in children) is almost always the result of direct personal contact. The gonococcus is quite restricted in its portal of entry. In human experiments, large quantities of virulent organisms have been injected subcutaneously without resultant disease.

Gonorrhea.—Most often involvement is limited to the mucous membrane of the anterior urethra in males and to the urethra and cervix in females. First evidence of disease appears two to six days after infection by sexual intercourse. In males there is usually much pain, and purulent exudate is readily apparent, exuding from the urethral orifice. In females, the exudate may remain hidden or obscured by a concomitant leukorrhea. Often there is little discomfort so that the individual may be unaware of her disease and of her infectious state. Since gonorrhreal vaginitis is rare in the adult, smears of vaginal secretion are of little value. Repeated examinations of urethral and cervical exudates may be necessary before the intracellular (polymorphonuclear) gram-negative diplococci are demonstrated. In uncomplicated cases, the infection remains limited to the superficial layers of the urethra or cervix, the purulent discharge gradually subsides and, within several weeks, there is spontaneous cure. Penicillin or sulfonamide therapy greatly accelerates this process and markedly decreases the incidence of complications.

If it were not for complications, the disease would be of relatively little consequence. In the male, the infection may extend beyond its usual confines, the anterior urethra, and involve the posterior portion of this passageway leading to *prostatitis*, *vesiculitis*, and *epididymitis*. Infection within the prostate may become chronic and lead to abscess formation. Such an individual remains infectious for a long period of time even though the amount of urethral exudate is slight. Sterility may follow epididymitis. Urethral stricture is a fairly common and important complication since it produces obstruction and this, in turn, markedly predisposes to ascending pyelonephritis. Complications in the female are more numerous and more

serious. Infection, with obstruction, of Bartholin's gland leads to abscess formation. The infection may extend from the cervix to involve the endometrium. Although gonococcal endometritis is not usually serious in itself, it allows for direct spread to the oviducts. These structures are highly susceptible to chronic gonococcal infection and the majority of cases of purulent salpingitis are of this cause. Tubo-ovarian abscesses and pelvic or generalized peritonitis may further complicate the picture. Acute gonococcal salpingitis with peritonitis may prove fatal. Chronic suppurative infection, i.e., pyosalpinx, is often responsible for a state of general ill health. Mechanical effects include sterility or a tendency toward ectopic pregnancy. Bacteriemia occurring during the course of the acute disease or secondary to some chronic focus occasionally results in endocarditis or arthritis. Pyemia has been observed. In gonococcal endocarditis, extensive ulceration with perforation of the affected cusps is common. Gonococcal arthritis is extremely painful and is usually polyarticular. Although the etiology of joint infection should be strongly suspected when it occurs in relation to recognized acute gonorrhea, the organism must be demonstrated in the synovial fluid for positive proof. In the majority of cases complete resolution occurs.

Vulvovaginitis.—The disease, as it occurs in children, is quite different from that just described. It is almost limited to girls and is usually a result of accidental contact with contaminated bedclothes, towels, etc. It occurs most often in institutions, and frequently assumes epidemic proportions. This susceptibility of vaginal epithelium in children is conditioned by the fact that, in the absence of significant amounts of estrogenic hormone, there is little keratinization. Treatment of the disease is greatly facilitated by the administration of estrogenic substance since this induces keratinization of the vaginal epithelium and a corresponding increase in local resistance. Occasionally epidemic vulvovaginitis in children is caused by *Staphylococcus aureus* and may be mistaken for gonococcal infection.

Especially in children, the gonococcus may cause a violent, acute purulent conjunctivitis which often results in corneal ulceration and permanent scarring. This may be a complication of vulvovaginitis, representing direct self-infection. *Ophthalmia neonatorum* occurs most commonly as a result of contamination incurred during passage of the baby's head through the birth canal. This used to be a very common cause of blindness. Its incidence is now extremely low because of a law, effective in most states, requiring the prophylactic instillation of silver nitrate into the eyes of every newborn infant.

Infections With Hemophilus Influenzae

Hemophilus influenzae (Pfeiffer's bacillus), a minute gram-negative rod, so short as to be almost coccal, often occurs in chains. It frequently exhibits marked pleomorphism. It is indistinguishable morphologically from *H. pertussis*. The species name, *influenzae*, was suggested by Pfeiffer in 1892 as a result of ob-

servations which led him to conclude, erroneously, that this was the causative organism of influenza. It is now established that influenza is caused by a virus and that the frequent association of *H. influenzae* with this disease is evidence of secondary infection. The genus name, *Hemophilus*, refers to the hemophilic nature of this group of organisms. Blood is a necessary part of their nutrient because it furnishes a coenzyme and also an iron-containing pigment from which the organism may synthesize cytochrome and related compounds.

H. influenzae normally inhabits the nasopharynx and tonsillar region of approximately 50 per cent of individuals, and infections with this organism are usually secondary to some other disease. Following a "cold" or other upper respiratory infection it commonly produces sinusitis or otitis media. *H. influenzae* pneumonia rarely occurs save as a complication of influenza. Dwinell (1919), in reporting a series of sixty-nine patients who died from pneumonia which complicated influenza and who were examined at autopsy, was able to recover *H. influenzae* in 49.3 per cent. Hemolytic streptococci were recovered in 59.4 per cent. Pneumonia produced by the influenzal bacillus is characterized by bronchitis, bronchiolitis, and patchy bronchopneumonia. Purulent exudate may fill the bronchioles and lead to bronchiectasis. This picture contrasts sharply with the interstitial pneumonia caused by *Str. pyogenes* which may also complicate influenza (see page 203). In infants and young children *H. influenzae* infection of the respiratory passages may produce marked edema, obstruction, and death within a few hours.

H. influenzae is responsible for approximately 3 per cent of cases of subacute bacterial endocarditis. Following bacteriemia it may, on occasion, produce a variety of acute or chronic pyogenic inflammations, e.g., cholecystitis and pyelitis. It is a major cause of meningitis, especially in children where it causes changes similar to those observed following other types of purulent meningitis. One of the most common causes of acute infectious conjunctivitis is the so-called Koch-Weeks bacillus, which organism is closely related to or identical with *H. influenzae*.

Infections With Bacilli of Proteus Group

These organisms are highly pleomorphic gram-negative bacilli which are actively motile. They are widely dispersed in nature, especially in relation to decaying meat and manure. They are commonly found in the feces of human beings, but in small numbers as a rule.

So far as disease production is concerned, there are two main species: *P. vulgaris* and *P. morganii*. These organisms are principally saprophytes. However, *P. vulgaris* often produces cystitis; frequently the organism can be recovered from the urine in pure culture. Because this organism produces ammonia from urea, infection is characterized by very alkaline urine. This may precipitate Ca, Mg, and NH₃ salts from the urine resulting in "alkaline encrusted cystitis." Otitis media is occasionally produced by *P. vulgaris* and is characterized by

rather widespread necrosis of both osseous and soft tissues. When these bacteria occur in abscesses, and in infected wounds and burns, it is usually as one component of a mixed infection. Their growth, under these circumstances, may favor the development of pathogenic anaerobes. In approximately 10 per cent of cases of appendicitis, proteus organisms can be recovered.

Proteus morganii was originally isolated from the stools of infants with summer diarrhea and ever since this time (1906) has been considered one of the etiological agents concerned with summer diarrhea. Many careful studies would indicate that there is no single specific bacterial etiology for this clinical entity.

Infections With *Pseudomonas aeruginosa*

This slender, gram-negative rod which varies considerably in length is the only member of the group *Pseudomonas* of medical importance. This organism is a common cause of wound infection and the nature of the infection is often recognized clinically by the greenish-blue color imparted to the purulent exudate. It was formerly called *Bacillus pyocyaneus* because of this property. A gangrenous myositis, somewhat resembling gas gangrene, has been described as the result of infection by *Ps. aeruginosa* in combination with anaerobic streptococci. Infections of the nasal fossae, middle and external ear are occasionally produced by this organism, especially in children. These tissues may undergo extensive necrosis leading to meningitis. Especially in infants and small children a serious form of pneumonia may be produced. Infection of the skin can lead to patchy areas of necrosis and ulceration sometimes referred to as ecthyma gangraenosum. The organism is occasionally responsible for pyelonephritis and also infection of the eye and of joints. Septicemia occurs rarely and this may be associated with endocarditis. It is stated (Pons) that in the tropics, the organism assumes much greater virulence and is capable of producing a systemic disease which resembles typhoid fever. As in the case of proteus organisms, *Ps. aeruginosa* has been recovered frequently from the stools of those suffering from summer diarrhea and is considered to be one of the etiological agents of this disease.

Infections With *Escherichia coli*

Escherichia coli (*B. coli*) is a gram-negative bacillus varying in form from a short coccobacillus to a long slender rod, indistinguishable from the typhoid, dysentery, and paratyphoid group of organisms except by cultural or serologic characteristics. It is a normal inhabitant of feces and the infections which it produces here are largely on the basis of opportunism. This organism is often considered together with *Ps. aeruginosa* and bacilli of the *Proteus* group since it produces pyogenic infections of similar type. Resultant purulent exudate is ordinarily grayish-green in contrast to the blue-green color which characterizes infection by *Ps. aeruginosa*.

It is of great importance as a cause of infections of the urinary tract where it ranks first in frequency. It often acts alone and may be recovered in pure culture. Frequently, however, there will be a mixed infection and an important component is *Str. faecalis* (group D, hemolytic streptococcus). Here, as in all ascending infections of the urinary tract, obstruction to the outflow of urine is an important predisposing factor. First there is infection of the bladder and cystitis may represent the total extent of bacterial involvement. Often, however, this is followed by ureteritis and pyelonephritis. (See page 578.)

Since *E. coli* normally inhabits the intestinal tract, it follows that fecal peritonitis will invariably include this organism as a part of the infectious mixture. Where there is mechanical injury, local injury from interference with blood supply (volvulus, obstructive appendicitis, diverticulitis, infarction of the bowel, etc.), or preliminary injury resulting from a primary hematogenous infection, *E. coli* avails itself of the opportunity provided and causes or contributes to infection.

In cholecystitis and cholangitis, *E. coli* is frequently demonstrable upon culture. However, there is evidence that cholecystitis is usually hematogenous in origin and that streptococci most often initiate the disease. The failure to find streptococci more often may be because bile inhibits the growth of this organism and culture of the bile fails to indicate the nature of infection within the wall of the gall bladder.

E. coli is an important cause of wound infection, especially in the region of the buttocks or thighs.

Toxemia from local infections with *E. coli* occurs most frequently in association with acute infections of the urinary tract and as a result of this there may be marked febrile reaction, malaise, etc. Septicemia very rarely occurs except in newborn infants. This condition, sometimes termed Winckel's disease, often runs a rapidly fatal course; it is analogous to the condition, white scour, which occurs in newborn calves. As with *Ps. aeruginosa*, the pathogenicity of the colon bacillus is considerably enhanced in tropical countries. There it is said to cause a systemic disease closely resembling typhoid fever.

Infection With *Klebsiella Pneumoniae*

Klebsiella pneumoniae (Friedländer's bacillus, *B. mucosus capsulatus*) is a short gram-negative encapsulated bacillus which often occurs in diplo-form in which case it appears rather similar to the pneumococcus. As with the pneumococcus, the capsule contains an antigenic polysaccharide which is responsible for type specificity; nucleoprotein contained within the body of the organism (somatic antigen) confers species specificity. Three principal strains have been isolated and defined, A, B, and C. A large group (group X) remains unclassified. Type B of *K. pneumoniae* is similar immunologically to type II pneumococcus. Protective antibodies are type specific. The organism inhabits the nasopharynx of 5 to 25 per cent of individuals.

Pneumonia caused by *K. pneumoniae* (Friedländer's pneumonia) probably accounts for ap-

proximately 1 per cent of all pneumonias although estimates of frequency range from 0.4 to 18 per cent. It most often affects those in the older age group and its occurrence is favored by any condition of general debility, including chronic

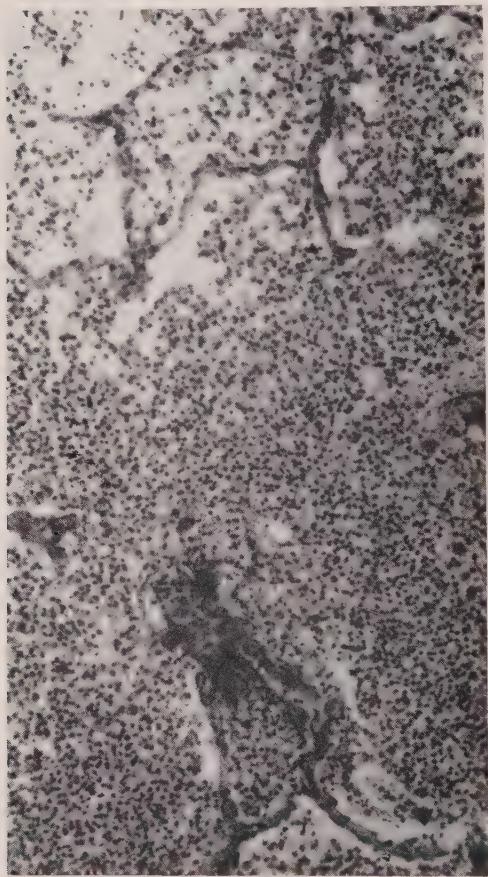


Fig. 146.—Pneumonia caused by *K. pneumoniae* (Friedländer's bacillus). Observe that in large areas the alveolar septa have undergone necrosis and dissolution. It is this characteristic which results in such a high incidence of complications such as organization rather than resolution, lung abscess, etc.

alcoholism. The early course of the disease, with its acute onset, resembles that of pneumococic pneumonia, but prostration is usually more marked and is often associated with pronounced dyspnea and cyanosis. The sputum usually contains more blood than in the case of pneumococic pneumonia and appears mucinous. There may be frank hematemesis. Organisms are readily seen in the sputum and are there in great abundance. Characteristically the lung presents an area of massive consolidation which may exceed the limits of a single lobe. Grossly, the picture is similar to that seen in pneumococic lobar pneumonia except that cut surfaces of the lung appear slimy and the lung parenchyma is friable. Histologically the major point of difference between this and ordinary lobar pneu-

monia is necrosis of alveolar walls. It is this effect which makes the lung friable and which markedly predisposes to such serious complications as lung abscess and organization. Fibrinous pleuritis is a characteristic feature of the disease and empyema is another complication to be feared. Bacteremia is readily detectable in over half of the cases and may lead to metastatic involvement of the meninges or joints. Septicemia with endocarditis has been observed. This may occur independently of pneumonia and often the source of infection is obscure. The mortality of Friedländer's pneumonia was formerly very high, averaging 70 to 80 per cent, and the majority of those who survived suffer major complications. Streptomycin and aureomycin are effective in treatment and have greatly improved the prognosis.

Chronic pulmonary infections with Friedländer's bacillus often arise secondary to chronic bronchitis or bronchiectasis, tuberculosis, influenza, or pneumonia. Occasionally, an acute pneumonia, caused by this organism, continues as a persistent chronic disease. This may lead to chronic abscesses, bronchiectasis, cavity formation, and extensive fibrosis. The condition often simulates closely pulmonary tuberculosis.

K. pneumoniae has been isolated from a wide variety of focal suppurative lesions, e.g., otitis media, salpingitis, subphrenic abscess and cholecystitis. An epidemic of infectious diarrhea in infants, which carried a high mortality rate, has been ascribed to this organism.

Rhinoscleroma, a very chronic and progressive granulomatous infection of the mucosa of the nose and pharynx has been attributed to *Klebsiella rhinoscleromatis*, but more recent studies suggest that this organism is identical with type C, *K. pneumoniae*.

A very persistent atrophic rhinitis, characterized by abundant encrusted, purulent discharge and a very foul odor is apparently caused by *Klebsiella ozaenae*. This organism shares the somatic antigen of *K. pneumoniae*, but has a different capsular antigen from A, B, or C.

Mixed Infections

"There is probably no concept fundamental to bacteriology that is as generally unappreciated and neglected as that of the existence of bacteria, both in nature and in the microcosm of the test tube, as populations."¹¹⁷ Our emphasis upon "pure cultures" and the properties of the individual organism tends to obscure the equally important properties and more complex problems presented by heterogenous bacterial populations.

Some diseases are produced only by specific combination of infective agents. The best known of these is Vincent's angina (or stomatitis), also termed trench mouth because of its high incidence among certain of the Armed Forces during World War I. It is the result of a mixed infection by a spirochete, *Fusobacterium spp.* (*Borrelia vincentii*) and a characteristic fusiform bacterium, *Bacillus fusiformis*. This mixture of organisms can be recovered from the oral cavity of a majority of apparently healthy individuals, hence predisposing factors must be in operation if infection is to occur. Since these organisms are anaerobic, the

presence of necrotic tissue, "pus pockets," etc., within the mouth is one predisposing factor. Characteristically the disease affects the tonsillar regions and the gums. Ragged ulcers may develop in the pharynx and the grayish-white membrane which covers them somewhat resembles that seen in diphtheria. The gums are usually swollen, reddened, and bleed easily; pus can often be expressed from the gingival margin. In aspiration pneumonia, these same organisms may produce focal areas of gangrene within the lungs or gangrenous laryngitis. Especially in malnourished and debilitated children this mixed fusospirochetal infection occasionally causes a progressive and usually fatal gangrene of the face, *noma* (*cancrum oris*). This frequently follows in the wake of such diseases as measles, diphtheria, malaria, and kala-azar. It begins on the inner aspect of the cheek or at the corner of the mouth as a purplish-red area and is soon followed by necrosis, blackish discoloration, and ulceration. This progresses to involve the entire thickness of the cheek. Another type of *infective gangrene* is that produced by a microaerophilic nonhemolytic streptococcus in association with a hemolytic *Staphylococcus aureus*. This most often follows wounds of the anterior abdominal wall and leads to progressive necrosis and ulceration. It has been termed *progressive bacterial synergistic necrosis*. A mixed infection by *Pseudomonas aeruginosa* and certain anaerobic streptococci may produce a gangrenous myositis which somewhat resembles that seen in gas gangrene.

SPECIFIC BACTERIAL DISEASES

The Bacterial Toxemias

There are several diseases in which bacterial toxins lead to profound systemic effects, effects which far overshadow those observed at the site of local bacterial infection. Diphtheria, tetanus, gas gangrene, and certain types of "food poisoning" are diseases of this type and warrant special consideration because of this peculiarity.

Diphtheria.—*Corynebacterium diphtheriae* (Klebs-Löffler bacillus) is a slender gram-positive rod which often presents club-shaped swellings at the poles and stains irregularly, giving the appearance of segmentation (metachromatic granules). It is the only organism of this class which is an important pathogen for man. Other species of *Corynebacterium*, the so-called diphtheroid group of organisms, though nonpathogenic, frequently inhabit the throat and the skin. Their presence and morphologic resemblance to *C. diphtheriae* makes it difficult to diagnose diphtheria by examination of throat or nasal smears alone.

In 1880, the death rate from diphtheria in this country averaged approximately 100 per 100,000 population. Today (1945), the death rate in the Northeastern part of the United States is 0.2 per 100,000. This is a result not only of effective therapy but of prophylaxis. Ramon's

discovery (1922 to 1924) of a safe method for inactivating diphtheria toxin without destroying its antigenicity provided an effective means for widespread active immunization against the disease. However, diphtheria has not lost its seriousness; one of the many catastrophes to affect Europe during World War II was a diphtheria epidemic of enormous proportions. Approximately one million cases occurred in the year 1943 and even more in 1944. In some areas, the mortality was exceedingly high.

The source of infection is principally by direct contact with human carriers although dust may contain organisms which remain virulent for several days. Approximately 1 per cent of the population harbor *virulent* organisms in their nose or throat; an additional 3 per cent carry strains of low or negligible virulence. Probably the most important type of carrier is the convalescent one. Usually repeated throat cultures will be negative two or three weeks after recovery from the disease, but approximately one individual in twenty will remain infectious after two and one-half months. Those with partial

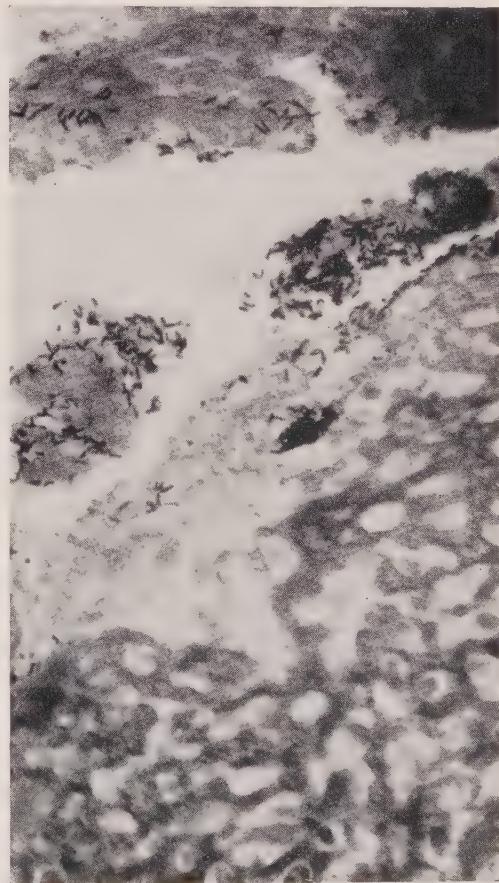


Fig. 147.—Diphtheria. The membrane which overlies the pharynx contains numerous *C. diphtheriae*. Observe that the infection is limited to the superficial layers of the mucosa. ($\times 1,000$.) (AFIP No. 67044.)

immunity to *C. diphtheriae* may develop a local infection accompanied by rather slight systemic manifestations. Since the diagnosis of diphtheria may not be suspected, these individuals represent a very serious hazard to public welfare. The infection usually begins in the oropharynx and often extends to the nose or larynx; occasionally it involves the respiratory tree. Rarely there is esophageal and gastric involvement as well. Other primary sites of infection include traumatic wounds or burns, the umbilical cord (diphtheria neonatorum), genital tract (post-partum or, in infants, following circumcision), and the conjunctiva. The onset of diphtheria is often insidious in contrast to acute tonsillitis with which it may be confused. It may be two or three days after initial symptoms of listlessness, malaise, and headache before the individual complains of sore throat. At this time the pharyngeal mucosa appears edematous and dark red. Cervical lymphadenopathy is present and may seem out of proportion to the observed pharyngeal changes. Marked cervical adenopathy is especially characteristic of severe forms of the disease. This appearance (bull neck) together with marked edema of the pharynx and sanguineous nasal discharge is forewarning of severe systemic manifestations. Soon, small white or gray patches appear in the pharynx, usually beginning in the tonsils. These patchy, grayish-white or blackened areas (depending upon blood content) enlarge and may become confluent with others which began on the palate. This is the characteristic diphtheritic membrane which is composed of leukocytes and numerous *C. diphtheriae* enmeshed in a dense network of fibrin. A superficial layer of the epidermis is necrotic, incorporated into the fibrin-rich exudate and densely adherent to it. This explains the tenacity of the membrane and accounts for the fact that when it is forcibly removed, adherent living epithelium is also stripped away leaving a raw bleeding surface. In the case of columnar epithelium, however (e.g., the nasopharynx and trachea), the pseudomembrane involves only a single layer of lining epithelium which is rather easily separable from its basement membrane. Portions of the dislodged diphtheritic membrane may be aspirated leading to asphyxia, atelectasis, or pneumonia. Tissues subjacent to this membrane exhibit edema, hyperemia, and various degenerative changes as a result of toxic injury. Since these local effects are the result of toxemia, it is not surprising that their severity tends to parallel that of systemic effects. When such a membrane involves the larynx it produces considerable mechanical obstruction; muscular spasm further contributes to the obstruction. It is this form of the disease which once carried such a high mortality. Today, the hazard of suffocation is largely eliminated by tracheotomy.

These mechanical effects are of relatively minor importance, in comparison with the profound toxemia which characterizes the infection. Direct assay of this toxin, in guinea pigs, is the only reliable method of determining the virulence of a given strain of the organism, and the lesions which are observed in guinea pigs resemble rather closely those which are

exhibited by human beings. The very marked toxicity of diphtheria toxin is reflected by the M. L. D.; less than one-ten thousandth of a milligram of purified toxin will kill a guinea pig and man is even more sensitive (per gram of body weight). Although several serologic types of *C. diphtheriae* have been established (I to V), more important are the types which relate to the amount and potency of toxin elaborated, *gravis*, *intermedius*, and *mitis*. These types have fairly well defined cultural and biologic characteristics and, as their names would indicate, produce disease of correspondingly grave, intermediate, or mild form. McLeod (1943), in summarizing data obtained from approximately 25,000 cases of diphtheria over a period of years, found that nearly half of the cases were produced by the *gravis* type and that the mortality (antitoxin treated) averaged 8.1 per cent as against 2.6 per cent for disease produced by the *mitis* strain. Antitoxin is effective in early treatment of diphtheria because first, it neutralizes circulating diphtheria toxin and also that toxin still retained at the site of its production; and second, by neutralizing the toxins produced at the site of local infection, it protects against further tissue necrosis and enables leukocytes to phagocytose and destroy the offending organisms which have very little invasive power.

Systemic changes are predominantly degenerative. However, *lymph nodes*, especially those draining the area of local infection, exhibit hyperplasia and contain large reaction centers which are in part necrotic. The *spleen* is hyperplastic too; Malpighian corpuscles are enlarged and contain large reaction centers. Approximately 80 per cent of cases of severe diphtheria will exhibit electrocardiographic changes between the seventh and tenth days. Grossly, the *heart* manifests cloudy swelling; microscopically there is interstitial edema and hyaline degeneration. Fat stains frequently reveal fine granules of lipid within the myocardial fibers and this change may be diffuse. Occasionally there is focal interstitial myocarditis with cellular exudation. This is most often localized to the subendocardial region of the apex and may lead to mural thrombosis with secondary embolic phenomena. Interstitial myocardial fibrosis may be a permanent effect, but usually recovery is complete. Approximately three-fourths of the deaths from diphtheria result from cardiac failure or peripheral vascular collapse. This is most likely to occur within the first two weeks of the disease, but may occur as late as the fourth week. Death may be a consequence of progressive heart failure with passive congestion of viscera, dyspnea, etc., but can also occur very suddenly as a result of ventricular fibrillation or asystole. Proteinuria is another almost constant finding and this is explained by the marked parenchymatous change observed in the *kidneys*. Acute nonsuppurative interstitial nephritis may be an effect of toxic (or allergic) injury; this usually resolves completely. The *liver* is characteristically enlarged and also exhibits cloudy swelling. Focal necrosis is common, but of little clinical significance. *Peripheral nerves* appear to have a special affinity for diphtheria toxin and the effects are de-

creased function leading to paralysis. There is degeneration or even destruction of the myelin sheaths. Axis cylinders appear swollen and rarely these too may be irreparably injured. The frequency and extent of paralysis tends to parallel the severity of the disease. Some degree of paralysis has been observed in as many as 20 per cent of a large series. Degenerative changes may also involve the brain, cranial nerves, cord, and nerve roots. In its mildest form paralysis is usually limited to the palate and leads to a peculiar nasal quality of the voice and a tendency to regurgitate fluids through the nose. If the paralysis involves the hypopharynx and the epiglottis, aspiration pneumonia is likely to occur. Occasionally there will be paralysis of the extraocular muscles or of the ciliary body, the latter leading to defective visual accommodation. Rarely, the extremities may become paralyzed and this may not occur until a month or so after the height of the disease. These changes are almost always temporary and usually disappear within two or three months after their onset.

Although paralysis, cardiac failure, etc., are often spoken of as complications of diphtheria, they are actually primary manifestations of toxic injury. The only serious complications, in the true sense of the word, are secondary infections, especially bronchopneumonia and otitis media.

Tetanus

Tetanus (lockjaw) is a disease which in its pathogenesis and general effects has much in common with diphtheria. The etiological agent is *Clostridium tetani*, a strictly anaerobic rather long, slender, gram-positive bacillus which often appears in the shape of a "drumstick" because of a large, oval, terminal spore. It is widespread in nature, especially in cultivated soil, since it is commonly found in the feces of cattle and horses and, to less extent, in man. Once an area is contaminated, the organisms persist, in spore form, almost indefinitely. Almost all mammals are susceptible to infection, but especially man and the horse.

Cl. tetani is a saprophyte, having practically no power to invade living tissue and infection cannot be accomplished without the assistance of a potent necrotizing exotoxin. This has been proved many times by injecting into animals (and human beings) large quantities of washed (toxin-free) spores, without untoward effect. It is further demonstrated by the occurrence of tetanus months or even years after healing of an initial wound, following superimposed injury. Since the organism is without invasive properties, it follows that tetanus usually occurs in relation to a wound. This may be of the type incurred in battle, with much laceration and destruction of tissue and gross contamination, or occasionally the disease follows such trivial injury as a scratch, blister, or hypodermic injection. *Cl. tetani* is a strict anaerobe; therefore puncture wounds, such as commonly result from a nail or splinter, are especially dangerous. Tetanus was once a common complication of abortion and was frequently seen also in infants (tetanus neonatorum) from in-

fection of the umbilical stump. In some primitive peoples it is said to have been responsible for the deaths of half of all children born. Under these circumstances, the organisms are usually introduced in the form of spores. The mechanisms by which the spores are activated is not completely understood, but the presence of free toxin is an important factor. Germination of these spores is stimulated also by concurrent infection with certain other bacteria (see page 212) and the presence of necrotic tissue or foreign particles. In the United States many cases of tetanus have occurred as a result of Fourth of July celebrations, especially following injury by shooting blank cartridges.

Tetanus is primarily a disease of nervous tissue, the result of injury by tetanus toxin. The site of local infection may be quite inconspicuous and in an appreciable number of cases it cannot be demonstrated at all. It requires a relatively slight infection to produce extensive injury since but little tetanus toxin is required for this effect. Tetanus toxin is considered to be the most powerful of poisons; less than a millionth of a milligram is sufficient to kill a guinea pig. Since absorption of tetanus toxin occurs rather slowly, there is a relatively great amount of toxin contained within the region of local infection and this may amount to many lethal doses. Because of this, one of the most reliable laboratory procedures to prove a diagnosis of tetanus consists of injecting wound scrapings, suspended in saline, into a guinea pig and watching for the characteristic toxic effects. The mere presence of tetanus organisms, as demonstrated by culture, is not diagnostic of the disease, since spores of *Cl. tetani* frequently contaminate wounds.

The effects of nervous tissue involvement in this disease are quite the opposite of those observed in diphtheria, where paralysis is the usual effect. In tetanus, the effects are comparable to those observed in strychnine poisoning with generalized and "regional" convulsions. Symptoms begin with headache and general depression, followed shortly by difficulty in swallowing and stiffness of the jaw, although for a short time muscle stiffness or spasm may be confined to the region of local infection, *local tetanus*. This soon progresses to the point where the jaw can be opened only with difficulty or not at all because of the marked spasm of the masseter muscles (trismus), thus the common name, lockjaw. Other muscle groups are affected too, especially those of the back, often leading to opisthotonus. Contracture of the facial muscles produces the characteristic *risus sardonicus* (doglike grin). Throughout all of this the patient is quite conscious and his ability to feel pain is, unfortunately, undiminished. As with strychnine poisoning, the stronger sets of muscles exert a predominant effect and generalized tonic convulsions are often precipitated by sudden noise or movement.

Mortality from the disease is somewhat related to the severity of the wound and the extent of laceration (necrotic tissue present). Wounds in the region of the shoulder girdle, upper extremity, and head carry a higher mortality. The incubation period varies from

a few days to a month. The shorter this period the more severe the illness.

Tissue injury is largely limited to the peripheral nerves and anterior horn cells. Morphologic changes are relatively insignificant and there are no characteristic diagnostic features. The exact mechanism by which tetanus toxin is distributed to these nerves is disputed. There is evidence to suggest that it is absorbed chiefly by the motor nerve endings, from which point it passes to the axis cylinders, finally reaching the anterior horn cells by direct transmission. Other evidence suggests that the toxin reaches the nerves via endoneurial and perineurial lymphatics, or perhaps by absorption directly from the blood stream. As with diphtheria, antitoxin is specific in the treatment of this disease, but there is one very important point of difference. In tetanus, nervous tissue has a very great selective affinity for the toxin, and shortly after it is absorbed it becomes fixed to this tissue so that no amount of antitoxin will neutralize it or undo the damage that has been already accomplished. For this reason, antitetanic serum (A.T.S.) is of limited therapeutic value. Today, the mortality from tetanus averages 40 to 50 per cent. It is much lower than this in the Armed Forces because antitetanic serum is usually given prophylactically so that in many cases, when the disease does occur, it is after a long incubation period and of relatively mild form. It is too early as yet to evaluate completely the effects of active immunization against this disease.

Gas Gangrene

No single bacterial agent can be held solely responsible for this condition. There are three members of the genus *Clostridium* which can each, independently, produce the disease; these are *Cl. welchii* (*perfringens*), *Cl. oedematiens*, and *Cl. septicum*. At least three other members of this class may contribute to the process although incapable in themselves of producing it. In infections which produce gas gangrene there is usually a mixture of these clostridia and, in addition, various aerobic organisms as well. The clostridia responsible for gas gangrene are strictly anaerobic, gram-positive bacilli and their growth is entirely saprophytic. These organisms are usually introduced into wounds as spores devoid of toxin and as such are incapable of growth and production of disease. They may therefore exist in wounds as contaminants without producing any effects. The factors which stimulate initial growth and production of toxin are not well understood in spite of considerable study. Concurrent infection with other organisms, notably *P. vulgaris*, may be sufficient to start the process (see page 212). Foreign particulate matter, especially dirt which contains soluble calcium salts or silicic acid, seems also to be effective. Once the organisms have begun to grow and to produce exotoxin, continuation of the process is assured. As the soluble toxin diffuses into surrounding tissues it produces an ever-expanding wave of necrosis; this provides dead tissue for additional growth of the clostridia, production of still more toxin, and so on.

In 1914, in the British Expeditionary Forces, approximately one man out of every thirty-five wounded died of gas gangrene! The incidence of occurrence was approximately 12 per cent. The major factor in reducing this tremendous morbidity and mortality was the adoption of new methods for local treatment of these battle wounds. It was soon learned that all dead tissue, debris, etc., must be completely excised, and that if, after such a process, the wound could not be properly closed with elimination of all dead space, then it had better be left completely open and allowed to "granulate in." Polyclonal antitoxin (against *Cl. welchii*, *oedematiens*, and *septicum*) proved to be of great value prophylactically as well as therapeutically, but it did not become generally available until the end of the war. In World War II, penicillin made a great contribution to the prevention and treatment of gas gangrene.

If gas gangrene is to occur, it usually becomes evident within a few hours to two or three days after injury. Tissues in the region of the wound are swollen, edematous, and painful, as a result of the increased tension. Often the process advances with great rapidity and soon the part becomes very tense and crepitant, because of numerous gas bubbles contained within the tissue. The skin is stretched tight and is dirty grayish yellow. From the wound itself or from rents in the skin, burst open because of internal pressure, there exudes a scanty serosanguineous fluid which contains numerous gas bubbles. Odor is usually not pronounced at this time, but soon the tissue becomes greenish-black and putrid. Gas gangrene, in its local involvement affects principally the muscles and it is these structures which show the most characteristic changes.

Robb-Smith and Govan have each made a detailed study of local changes in gas gangrene. Govan emphasizes striking differences between the "mild" and "severe" cases. In both types there is necrosis involving all elements adjacent to the wound surface. Ordinarily muscle fibers undergo coagulation necrosis, but occasionally they liquefy. Large gram-positive bacilli are present in great numbers. In the mild form there is a zone of intense leukocyte reaction and congestion with no evidence of spread of infection to surrounding tissues. This appearance contrasts sharply with the severe form in which there is practically no leukocytic response; about the region of frank necrosis there is a wide zone of edema and congestion. Muscle fibers become widely separated from each other as do the interstitial connective tissue elements. Although striations may be visible in many muscle fibers, nuclei are pyknotic or absent altogether. The sarcolemma is fragmented and seems to be dissolving. There are numerous hemorrhages and many of the widely dilated capillaries and venules are thrombosed. According to Govan, it is this zone of congestion and thrombosis which marks the periphery of the spreading lesion and he suggests that capillary and venous thrombosis is one of the main factors allowing the spread of gas gangrene in muscle.

Systemic reactions are marked in the severe cases and there is fever, tachycardia, prostra-

tion, and, terminally, peripheral vascular collapse. The potent hemolytic toxins may account for a marked drop in red blood cells. Terminally, the organisms invade the blood stream and are widely distributed to all tissues. There is marked pulmonary edema and hyperemia and evidence of profound injury is to be found in almost all organs, especially the kidney. There is question as to whether this is from bacterial toxins or from breakdown products of necrotic tissue. Govan has described widespread fat embolism in persons dying of gas gangrene and he attributes this to the action of *Cl. welchii* toxin (lecithinase) on adipose tissue or blood lipids. If the postmortem examination is delayed a few hours, gross evidence of gas formation is evident in most organs. These crepitate upon pressure and the liver especially may present a honeycomb appearance. Changes of this marked degree are the result of bacterial growth which

under natural conditions. In spite of this fact, however, it has caused many deaths. The organism is a common soil anaerobe of the western United States and so the contamination of food-stuffs, especially vegetables, is a common occurrence. *Cl. botulinum* is quite resistant to heat; spores may withstand dry heat up to 180° C. for as long as fifteen minutes. If proper precautions are not taken in the preservation of food, conditions may develop which are quite favorable to growth and toxin production by this organism. As a matter of fact, inadequate cooking favors the growth of this organism since other, less heat-resistant bacteria are killed and cannot therefore overgrow and inhibit *Cl. botulinum*. Furthermore, the destruction of these other organisms often prevents obvious spoilage and the warning signs of bad odor and color. Home-canned vegetables, especially nonacid ones such as beans and corn, are the most common sources



Fig. 148.—Gas gangrene. A, Observe numerous *Cl. welchii* and necrosis of muscle fiber. B, Note large gas-filled spaces and also separation of individual muscle fibers from their sarcolemmal sheaths. (From Berman, Synopsis of Surgery, The C. V. Mosby Co.)

has continued after death of the host. *Cl. welchii* and related organisms are occasionally responsible for puerperal sepsis, especially following criminal abortion. The mortality rate is very high and systemic manifestations are marked.

Food Poisoning: Botulism, Staphylococcal Food Poisoning and Infection With Certain Salmonella Organisms.—Two types of "food poisoning" are concerned with bacterial infection. One type results from the ingestion of preformed toxins and is not an infection. The other type occurs less frequently and is more properly termed "food infection" since it results from ingestion of viable bacterial organisms which set up infection in the gastrointestinal tract.

BOTULISM.—*Clostridium botulinum* is an anaerobic bacillus which is nonpathogenic for man

of botulin toxin, although preserved meats (smoked ham, sausage, etc.) have been responsible for the disease in many instances. The term botulism was derived from the Latin word meaning sausage, since large outbreaks of this disease were first observed following ingestion of improperly cooked sausage. No outbreak of botulism has been attributed to commercially canned foods packed in the United States since 1925. Sporadic cases, attributable to improper home canning, continue to take a yearly toll.

As with diphtheria and tetanus, we are here concerned with a poison which is extremely potent; a very little goes a long way. The mortality from botulinus toxemia is very high; of 1,024 cases collected by K. F. Meyer, 65 per cent died. Symptoms may begin within three or four hours after ingesting the toxin, but more



Fig. 149.—Acute endometritis and myometritis—puerperal sepsis. Note the interstitial hemorrhage and the soggy, spongy appearance which is characteristic of infection by *C. welchii*.

often onset occurs between twelve and thirty-six hours. Depending somewhat upon the dose, there may be nausea and vomiting, or perhaps only a sensation of burning and abdominal distress. Colic or abdominal tenderness is not observed. Diarrhea sometimes occurs initially, but constipation is the more often a complaint, occurring early and persisting throughout the course of the disease. Muscular paralysis is one of the most characteristic signs and it is usually not until this is observed that the diagnosis is suspected. Difficulty in swallowing and/or diplopia are the first changes of this sort. If the disease progresses, there is paralysis of the pharyngeal muscles, so that when the patient attempts to eat or drink, the material is regurgitated through the nose. This may lead to aspiration pneumonia, a frequent and important complication. Further involvement of ocular muscles results in loss of light reflex, mydriasis, nystagmus, and occasionally vertigo. Among the other muscles, those of the neck are

the most often affected and the patient may be unable to hold his head erect. Throughout all of this, the temperature remains normal or subnormal. Death, if it occurs, is usually from respiratory failure. Specific antitoxin is the only aid and it is of most value early. Once the disease is well established the toxin is firmly bound to the nervous tissue and can no longer be neutralized by specific antiserum.

The toxin acts somewhat like curare, affecting principally the end plates of nerves, specifically the myoneural junctures of the motor apparatus. There are few specific morphologic changes in this disease. The brain stem and meninges may exhibit hyperemia, minute hemorrhages, and thrombosis of multiple small veins.

STAPHYLOCOCCIC FOOD POISONING.—Since it is not required to report this disease to the public health authorities, accurate information as to its frequency is not available. It is probably the most common type of food poisoning, however. It differs considerably from botulism in that symptoms appear rapidly and are of relatively short duration. Recovery is usually prompt and complete. The incubation period averages three hours and rarely falls beyond the limits of one to six hours. Excessive salivation is often the first sign, followed shortly by nausea and vomiting with marked retching. Severe abdominal cramps and diarrhea soon complicate the picture and the individual is "deathly ill." In very severe cases, blood and mucus may appear in the stools. Occasionally death results, but recovery is the rule.

For the production of this disease. (a) food must be contaminated by a strain of staphylococcus which produces enterotoxin; (b) the type of food must be suitable for growth of this organism; (c) the infected food must be kept at a temperature suitable for bacterial growth and sufficiently long that an appreciable quantity of enterotoxin is formed. These conditions are most commonly met in the case of cream-filled bakery goods, but other products such as "ready to eat" ham or tongue may be similarly involved. In contrast to *Botulinus* toxin which is completely destroyed by vigorous boiling for ten minutes, staphylococcus enterotoxin is extremely resistant to heat. It is also quite stable so far as time is concerned and will persist in foods stored in the refrigerator for very long periods. Clinical manifestations of this disease are quite characteristic and usually suffice to establish the diagnosis. Final proof by laboratory confirmation is difficult to achieve. Since the disease is nonfatal, morphologic changes have not been described.

INFECTIONS WITH CERTAIN SALMONELLA ORGANISMS.—There has been much confusion regarding this condition, and many outbreaks of food poisoning, attributed to infection with this organism, have probably resulted from ingesting staphylococccic enterotoxin (Dow). This condition is not a toxemia but is a gastroenteritis resulting from *bacterial infection*. As might be expected with an infectious disease, the incubation period is considerably longer than in the case of staphylococcus food poisoning, twelve- to twenty-four hours as a rule. The onset is sudden and sometimes a chill will be the initial symptom,

There is headache, nausea and vomiting, severe abdominal cramps, and marked prostration. Three characteristics which help to differentiate this from poisoning with staphylococcal enterotoxin are: muscular weakness, fever, and persistent very foul-smelling diarrhea. A positive diagnosis is best made by demonstrating the *Salmonella* both in the stool and in the food. Two organisms are most commonly responsible for this infection: *Salmonella typhimurium* and *Salmonella enteritidis*. Foods become infected with these organisms principally in two ways. In animals, especially those slaughtered because of disease, there may be widespread dissemination of the organisms as an effect of terminal bacteremia or septicemia. Much more often, however, foodstuffs become infected with *Salmonella* organisms as a result of contamination during the time of processing or display. Meat and eggs have been common offenders. Rats and mice may harbor *Salmonella* organisms in their intestinal tract, and their droppings provide a direct means for infecting various foods. Human carriers are important too.

Although there is a high morbidity among persons who suffer from this type of food infection, mortality is very low, between 0.3 and 0.5 per cent. Morphologic changes, according to the very few postmortem studies available, include a diffuse gastroenteritis and parenchymatous degeneration of many organs. The liver may exhibit focal necrosis and fatty change.

Typhoid and Paratyphoid Fevers (Enteric Fever)

Thirty years ago, the treatment of typhoid fever provided the major income of many physicians. The very marked decline in incidence of this disease represents one of the great triumphs of preventive medicine. In 1910, 20.54 persons per 100,000 population died of the disease. This figure was reduced to an average of 0.6 for the period of 1940 to 1945. Although typhoid fever is now comparatively uncommon in this country, occasional epidemics and sporadic cases continue to take their toll. As our vigilance relaxes and a progressively increasing number of persons neglect the precaution of active immunization, new and large epidemics may be expected as a reminder that *Salmonella typhosa* is a highly pathogenic organism for man. *S. typhosa* is a short, plump, gram-negative rod which is flagellated and actively motile. It is indistinguishable morphologically from other members of the enteric group. Its relative lack of resistance to common antiseptics, drying, sunlight, and heat is one reason why sanitary measures have been so effective in controlling the disease. Infection occurs directly or indirectly from an individual afflicted with or convalescing from the disease, or from a healthy carrier. Contaminated food or water is the common medium of contagion. The five F's most concerned with spread of this disease are: food, fingers, flies, fomites, and feces. Urine is often a more important source of infection than feces since contamination of the hands is more likely to occur following urination and the urine is more likely to be "deposited" in an unsuitable

container, or on the ground. Then, too, in those whose typhoid fever is complicated by "pyeloureteritis," the number of organisms passed in the urine is greatly in excess of those commonly found in the feces.

S. typhosa is, for all practical purposes, restricted in portal of entry to the gastrointestinal tract. It has been injected subcutaneously without harm and, as a matter of fact, some vaccines contain viable organisms. Upon penetrating the intestinal mucosa, the organisms quickly enter lymphatic vessels and mesenteric nodes from whence they reach the liver and then, via the thoracic duct, the blood stream. All this occurs in the quiescent or incubation period, usually ten to fourteen days. This is the first stage of the disease in which generalization of the infection occurs before localizing lesions draw attention to the intestine.

In the second stage of the disease there is severe headache, generalized aching, especially



FIG. 150.—Typhoid fever—ulceration of ileum. Note that these ulcerative lesions of the ileum correspond in location to lymphoid follicles and Peyer's patches. Where they occur in Peyer's patches (right side of photograph) observe their oval shape with long axis parallel to that of the intestine. (AFIP No. 2803.)

of the arms and legs, malaise, and fatigue. Shortly thereafter the picture changes to one of frank septicemia with chills, fever, prostration, splenic enlargement, and the rather characteristic *rose spots*. These latter usually occur during the second week of the disease and at first glance resemble petechial hemorrhages. The fact that they blanch on pressure reveals them to be an effect of marked hyperemia (capillary atony). Aggregations of macrophages and edema in these focal areas indicate that they represent sites of bacterial localization (embolization) and resultant local toxic injury. They disappear after a few days. The *third stage*, after a week or ten days, is dominated by effects of local bacterial injury, especially in the intestinal tract, mesenteric lymph nodes, spleen, and liver. Last is the *stage of lysis* in which the infectious process is gradually overcome. Symptoms slowly disappear and the temperature gradually returns to normal. These four phases of the disease and their significance are illustrated in Fig. 151.

to Peyer's patches. In the colon, ulcers are smaller and punctate, corresponding to the smaller lymphoid follicles there. Microscopically an outstanding characteristic is the lack of polymorphonuclear leukocytes. The predominant cell of reaction is a large monocyte (macrophage) which somewhat resembles the blood monocyte. These are present in abundance in the base and margin of the ulcer. Lymphocytes and plasma cells are seen too. *Lymph nodes* exhibit foci of necrosis which may be as large as several millimeters in diameter. There is marked proliferation of the sinusoidal cells and sinusoids are filled with macrophages similar to those observed in the intestinal ulcers. This picture is almost pathognomonic of typhoid fever. The lack of participation by polymorphonuclear leukocytes is reflected by the absence of leukocytosis. In fact, *leukopenia* is characteristic and an important clinical sign since very few bacterial infections are associated with a low white blood cell count.

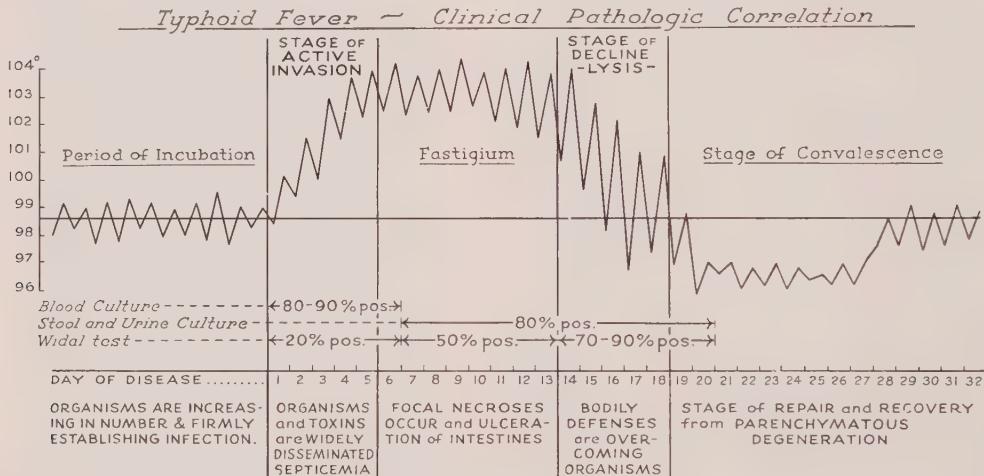


Fig. 151.—Typhoid fever. Clinical pathologic correlation (chart).

Although septicemia dominates the early stages of typhoid fever, significant local changes begin to occur at this time, first in the lymphoid tissue of the intestinal tract. *Peyer's patches* of the ileum and the solitary lymph follicles in the region of the cecum become hyperplastic and so swollen as to produce almost buttonlike protrusions. The *mesenteric lymph nodes* become markedly hyperplastic too, as a result of infection via lymphatics and *S. typhosa* can usually be recovered in pure culture from these mesenteric lymph nodes. Along with this, the *reticuloendothelial system* as a whole is responding to the septicemia and there is hyperplasia of other lymph nodes, the spleen, reticular elements of the bone marrow, and von Kupffer cells of the liver. After seven to ten days, the picture in the intestine is complicated by necrosis and ulceration of those areas which formerly exhibited lymphoid hyperplasia. Long oval ulcers in the ileum are parallel to the long axis of the bowel and correspond in shape and arrangement

among other organs most marked changes occur in the spleen and liver. The *spleen* is markedly enlarged, frequently weighing 800 or 900 grams. Its capsule is tense and the parenchyma mushy (diffused). The organ is so soft and swollen that occasionally it ruptures during removal at autopsy; splenic rupture rarely occurs "spontaneously" during life. The striking cherry-red color is reflected microscopically by marked hyperemia. There is marked hyperplasia also, especially of the red pulp. Areas of focal necrosis are seen, similar to those observed in mesenteric lymph nodes. The *liver* also is enlarged and swollen, as evidenced by the tense capsule and rounded edges. It presents the picture of marked cloudy swelling. Parenchymatous degeneration is evident microscopically and focal necrosis is a characteristic finding. The distribution of these minute foci bears no constant relation to the architecture of the hepatic lobule; some will be found peribularly, others adjacent to the central vein, and

still others midway between. This is in striking contrast to the *zonal* necrosis of yellow fever, eclampsia, chloroform poisoning, etc. Formerly these areas were considered to be analogous to tiny infarcts, a result of embolization by agglutinated bacilli. This has been disproved and it appears that the primary reaction is not one of degeneration, but an *aggregation of macrophages* which have come from the intestine (portal vein). As these continue to accumulate, the capillaries are markedly distended and liver cords compressed. It is *after* this that some necrosis of hepatic cells may occur, perhaps from a combination of injuries—pressure, toxic effect, and ischemia. It would seem better to term this lesion the *typhoid nodule* since necrosis is not the primary nor the outstanding feature. This is a characteristic reaction of typhoid fever and occurs in lymph nodes, spleen, and bone marrow, as well as the liver. The heart and kidneys show cloudy swelling as a manifestation of toxemia. This change in the heart is reflected by a persistent bradycardia (an important diagnostic sign) which appears so out of place considering the patient's fever. Skeletal muscles are particularly susceptible to these toxins and exhibit a marked degree of Zenker's (waxy) degeneration. As is the usual case, this nonspecific degenerative change affects principally those skeletal muscles which are most active when the patient is at rest—intercostals, diaphragm, and rectus abdominis. This damage is occasionally so marked as to lead to rupture of the rectus muscles with pain, hemorrhage, etc. This may simulate "acute surgical abdomen" and lead to surgical exploration.

There are many other complications from this disease. Most feared is massive intestinal hemorrhage and this occurs in from 5 to 10 per cent of instances. Of next importance is the complication of peritonitis from perforation of the bowel. The most common site is the terminal ileum and this is most likely to occur during the second or third week. When perforation of the intestine occurs, the resultant *fecal* peritonitis is usually fatal. Rupture of a mesenteric lymph node will produce a specific *S. typhosa* peritonitis which is less severe and from which the patient often recovers. Intestinal obstruction, as a sequel to ulceration, rarely occurs because there is relatively little scar formation upon healing. Since typhoid fever is a septicemic disease, focal metastatic infections can develop in a variety of places and may be responsible for osteomyelitis, meningitis, endocarditis, or nephritis. In approximately 5 to 10 per cent of cases there occurs a thrombophlebitis of the femoral or saphenous veins. This rarely develops before the fourth week and comes at a time when the patient appears well on the road to recovery. Infection of the gall bladder occurs almost invariably. This poses a special problem if the resultant *cholecystitis* becomes chronic, leading to a persistent carrier state. Focal *paralysis* sometimes occurs and this seems to be an effect of toxemia. Relapses occur in 5 to 10 per cent of the cases. Death may result from one of the complications previously described, but often simply from typhoid fever per se. This terminal phase is one of marked debility and wasting, but most characteristic are the mental

signs and symptoms. The individual is semi-stuporous and yet very restless, nervously plucking at the bedclothes and groaning. The mortality, formerly 10 to 20 per cent, has been reduced by use of chloramphenicol and aureomycin.

Typhoid fever is one of the most protean of all bacterial diseases and often the diagnosis does not become apparent until late in the course, or perhaps until autopsy. For this reason laboratory procedures are usually depended upon to confirm or disprove a suspicion of typhoid fever. Fig. 151 shows the place of blood culture, serologic studies, and bacteriologic examination of feces and urine in establishing the diagnosis. Agglutination tests (Widal test) for typhoid fever deserve a further word of explanation. The serum of most individuals has the capacity of agglutinating typhoid organisms at a dilution of at least 1:50. If one has been immunized against the disease, his serum antibody titer may be considerably higher. For this reason, interpretation must be made on a *quantitative* rather than a qualitative basis. In addition, because of the close antigenic relationship which exists between *S. typhosa* and those organisms that cause paratyphoid fever it may be very difficult to differentiate between these diseases by serologic means. It is of considerable value to determine antibody response against different antigenic fractions of these organisms, namely O (somatic) antigen, H (flagellar) antigen, and Vi antigen. Some individuals with typhoid or paratyphoid fever develop antibodies against O antigen only, and furthermore, titers to O antigen disappear more quickly and usually do not reach the height of H titers as a result of active immunization. It follows therefore that antibodies against O antigen (above 1:50) are most significant in establishing the diagnosis of infection. On the other hand, the titer against H antigen is more helpful in determining which of the typhoid-paratyphoid group of organisms is responsible for the infection (Topley and Wilson). Agglutination titers against Vi antigen are always low, but specific. They are diagnostic if it is known that the patient is not a typhoid carrier (Smith and Martin).

Paratyphoid fever is caused by *S. paratyphi* A, *S. paratyphi* B or *S. paratyphi* C. This disease is in essence a "miniature" typhoid fever. There are no significant differences from typhoid fever except in the severity of symptoms and the frequency of complications.

Bacillary Dysentery

The term dysentery (Greek, painful disease of the bowel) was once used synonymously with "bloody flux" and applied to any condition of painful diarrhea in which the stools contained blood and mucus. Since this description may fit diseases caused by bacteria, protozoa, helminths, chemical or bacterial toxins, allergy, etc., the word dysentery means little in terms of specific disease. Today it is rarely used without proper prefix, e.g., bacillary, amebic, etc. Bacillary dysentery has been one of the most constant scourges of wars, and it has been the deciding factor in many battles. Under conditions of war, the mortality rate from this

disease has been as great as 50 per cent though ordinarily (before sulfonamide therapy) it caused death in but 4 or 5 per cent of those afflicted. Clinically, it presents many degrees of severity to which the terms mild or catarrhal, acute, fulminant, relapsing, and chronic have all been applied (Manson-Bahr). During the four years, 1940 to 1943, inclusive, an average of approximately 25,000 cases of bacillary dysentery occurred each year in the United States. During this period there were approximately one-third this many cases of typhoid and para-typhoid fevers. Four main groups of organisms are responsible for bacillary dysentery and these are all short gram-negative rods which are nonmotile and devoid of flagella: *Shigella dysenteriae* (Shiga bacillus), *S. ambigua* (Schmitz bacillus), *S. paradysenteriae* (Flexner and Boyd types) and *S. sonnei*. These organisms are derived from human sources and infection occurs most often from eating contaminated food.

pain soon makes its onset and this is accompanied by diarrhea and tenesmus. Largely depending upon the degree and location of intestinal lesions, tenesmus can be most distressing. This is particularly so if the ulcerative lesions involve the rectum, in which case even death may occur as a result of the exhausting labors of almost continuous violent straining at stool. The character of the stool is influenced by the frequency of bowel movements. At first, the stool is abundant, watery, and fecal. Soon the frequent urges to empty the bowel may do just that so that subsequent movements are scanty in amount and consist mainly of bowel tissue itself, slimy, bloody, or blood-stained mucus with flecks of fibrinous and purulent exudate. The diarrhea may attain a frequency of 50 to 100 times a day, rapidly exhausting the patient, depleting him of water, and quickly producing a state of electrolyte imbalance.



Fig. 152.—Bacillary dysentery, large intestine. (From Anderson, Synopsis of Pathology. Courtesy Dr. H. C. Schmeisser.)

After an incubation period of a few hours to a day or two there is sudden onset of fever, headache, and malaise. These usually precede abdominal pain and diarrhea by several hours or even a day or two. The organisms can but rarely be demonstrated by blood culture and it appears that the infection is a local one limited to the intestine. We are likely to think of this condition in terms of its effect on the intestines. However, in the case of *S. dysenteriae* effects of toxemia may dominate the picture. This is particularly true in children in whom symptoms and signs may closely simulate meningitis, and the child may die during a convulsive seizure. Adults, too, often have central nervous system symptoms, e.g., drowsiness or perhaps stupor. These symptoms and the meningeal form of the disease occur only with infection by *S. dysenteriae* since only this organism elaborates a potent neurotrophic exotoxin. In the usual case, however, abdominal

Principal changes occur in the ileum and colon. At first there is a diffuse hyperemia and edema with hyperplasia of lymphoid tissue. Within a few hours this has progressed to patchy areas of very superficial necrosis which become overlaid with a thin gray fibrinous membrane resembling that seen in diphtheria, but thinner. This is followed by superficial ulceration and these shallow lesions are of various sizes and shapes. Unlike those of typhoid fever they are not confined to regions of lymphoid tissue. The ulcers remain shallow unless secondarily infected. Unfortunately this often occurs and secondary infection may cause much local tissue destruction and contribute seriously to the chronicity of the case. Even so, perforation seldom occurs. In the stage of ulceration, microscopic examination reveals diffuse edema of the submucosa which is infiltrated with inflammatory cells, principally macrophages and

plasma cells. Polymorphonuclear leukocytes are seen mainly in the mucosa proper and probably represent reaction to secondary infection. There is marked hyperemia, capillaries and venules are thrombosed, and numerous small hemorrhages are seen. The superficial layers of the mucosa are necrotic and overlaid with a layer of fibrinous exudate. Those goblet cells deep in the crypts are stimulated to hypersecretion and there is abundant mucus. Many superficial ulcers are seen. These usually heal and the involved areas become covered with a simplified epithelium. Mucous glands may become buried as a result of this and their continued secretion leads to formation of small mucous cysts, up to 2 to 3 mm. in diameter. These rupture in time and, since they often contain viable *Shigella*, may result in "re-infection" of the patient or spread to others. In those with central nervous system symptoms, one may find degenerative changes and minute hemorrhages in the brain and cord somewhat resembling the picture of acute anterior poliomyelitis (Ash and Spitz).

A complication especially to be feared is that the condition will persist in a chronic form, from which it may gradually merge into *chronic ulcerative colitis*. Occasionally bacteremia does occur and there may be localization and infection in the kidney, the joints and, in rare instances, the heart (endocarditis).

Cholera (Asiatic Cholera)

Cholera is rare in this country, but is responsible for nearly half a million deaths each year in India. Because of its acute onset and very rapid course leading to a state of marked exhaustion, dehydration with severe muscular cramps, etc., it was long ago differentiated from other diarrheal diseases such as typhoid fever, bacillary, and amebic dysentery. An excellent description of the disease may be found in the Chinese medical literature as early as 430 B.C.

The disease is caused by *Vibrio cholerae* (comma bacillus), a short, curved, or comma-shaped bacillus which is gram negative and actively motile. It gains entrance to the body principally by means of contaminated food or drink. *V. cholerae* is adapted to an environment provided by soil or water and it can persist in viable form, in water, for as long as seven days. When a major water supply is contaminated, the resultant epidemic will be explosive in its origin and extent. The many pandemics which have ravaged Asia and Europe have cost millions of lives and have been so extensive as to involve almost all of Europe and Asia at one time. The great pandemic of 1826 to 1837 spread also to America as a result of immigration of infected persons.

The manifestations and course of the disease are readily explained on the basis of two major effects: (1) toxemia from the powerful *endotoxins* released upon death and lysis of *V. cholerae*, and (2) dehydration with depletion and imbalance of minerals as a consequence of profuse diarrhea and vomiting. Following an incubation period of one to three days, symptoms make a recititous onset, dominated by a very copious and purging diarrhea. Within a few hours this is accompanied by vomiting, severe

muscle cramps, and general prostration. At first the stools contain dilute, fluid feces, but as soon as the intestine is flushed out, all fecal content disappears and the frequent movements appear like water in which numerous flakes of grayish-white mucus are seen—the so-called rice-water stool. This, together with vomiting, soon leads to a most profound state of dehydration in which the skin is coarsely wrinkled, the eyeballs sunken, and all mucous membranes dry and sticky. This is the so-called *algid* state (L, cold) in which there is peripherovascular collapse, cyanosis, and subnormal temperature, sometimes as low as 70° F! Six to seven liters of fluid per twenty-four hours may easily be lost in the stools alone, affecting marked depletion of minerals as well as water. It is stated that more than 50 grams of NaCl may be lost in a day. The extent of dehydration is revealed by blood studies in which red blood cells may reach 8,000,000 per cubic millimeter with the hematocrit as high as 75 to 80 per cent. Blood specific gravity, normally 1.056 to 1.058, may be increased to as much as 1.065. Needless to say, urinary secretion is *nil* during this time and signs of uremia, including acidosis, further complicate the picture. Occasionally, the effects of toxemia are so profound that the patient enters into a state of collapse within several hours from onset of the disease and dies before the development of diarrhea or its attendant effects of dehydration. However, the majority of deaths occur during the *algid* stage and within twenty to thirty hours from onset of the disease. If the patient survives this most critical period he enters the so-called *stage of reaction* in which blood pressure and normal color are gradually restored. The feeling of coldness decreases and stools diminish in number. Death may still come at this stage, however. Frequently, urinary function will not be resumed and the patient dies of uremia. Before antibiotic therapy, the mortality ranged from 50 to 60 per cent unless great care was directed toward restoration of fluid and mineral deficiencies as they developed.

Morphologic changes in the intestine are relatively slight. The infection is a very superficial one. The intestine exhibits diffuse hyperemia, edema and, areas of superficial erosion. If death occurs during the *algid* stage, the most striking change is the very marked dehydration of all tissues. Hemoconcentration is evident in the dark thick blood which oozes from cut tissues. *Rigor mortis* comes on quickly and is often dramatic, resulting in marked distortion of limbs.

Brucellosis (Undulant Fever, Mediterranean Fever, Malta Fever)

The serious aspects of brucellosis, as it exists in the United States, have been generally appreciated only in the last few years. In spite of its high incidence, brucellosis escaped proper notice before this time because of its protean nature and because of the many diseases which it commonly simulates, notably typhoid fever, tuberculosis, malaria, some hidden focus of pyogenic infection, appendicitis, cholecystitis; often it has paraded under the name neurasthenia. Three different members of the genus

Brucella may cause the disease and each of these has a different animal reservoir. The caprine strain (goat), *Br. melitensis*, is very prevalent in the Island of Malta and the Mediterranean area from whence came the original name of Malta fever or Mediterranean fever. It is the least common cause of brucellosis in this country, though said to be prevalent in Texas, Arizona, and California. The bovine strain (cow), *Br. abortus*, is widespread among the dairy herds of this country and in cattle produces what is commonly known as Bang's disease, or contagious abortion. The porcine strain (pig), *Br. suis*, is responsible for the majority of human infections in the United States. In each of these animals, symptoms commonly result from infection by brucella organisms. The predominant effect is that of abortion, but there may also be mastitis, lameness, and, especially in swine, vertebral abscesses. Sheep, horses, dogs, rats, guinea pigs, cats, and birds may be infected by and harbor Brucella. These organisms are small gram-negative coccobacilli which are difficult to cultivate upon artificial media and slow to grow. The natural host of each of these organisms is a common domestic animal and man contracts brucellosis as a result of his contact with these animals or their products. It has been demonstrated that the organisms may pass through the unbroken epidermis, thus the disease is a serious occupational hazard to meat packers, farmers who raise hogs and cows, and laboratory workers who handle the organisms. Ingestion of infected milk is probably the most important means of contracting the disease, but the widespread practice of pasteurization has greatly curtailed the incidence of infection by *Br. abortus*.

Because of the marked variations in the disease it is almost impossible to describe all the forms which it may assume. One clinical classification is according to acute, subacute, or chronic form. In another classification three clinical types are based primarily on differences in temperature curves. These are: the *malignant*, the *undulant* (intermediate in severity), and the *intermittent* (persistent chronic form). Since the disease is a *septicemia*, general manifestations may be complicated by a wide variety of focal metastatic lesions. In this country the *intermittent type* is most common. The incubation period varies between ten and ninety days and, especially in the *intermittent type*, the patient may be unaware of any specific time of onset, rather complaining of progressive tiredness and malaise, inability to work effectively, etc. Along with this there develops mental depression and generalized aching, especially of the head and back. Frequently there will be rheumatic type pains, often in the sacroiliac region or in the form of sciatic neuritis. The patient usually complains also of constipation and insomnia. After a while, fever with night sweats may be a distressing feature. Temperature, usually near normal in the morning, rises to 101° to 104° F. in the late afternoon or evening. The *undulant type* of brucellosis is caused almost always by *Br. melitensis* and so is less common in this country. It is characterized by an undulating fever, gradually reaching its peak in four to seven

days, persisting thus for a week or so and then, in a few days, gradually subsiding. These periods of fever, two to three weeks in duration, alternate with a week or two of relatively normal temperature and this reaction may continue for three months to a year. The *malignant type* is quite uncommon. Following sudden onset there is high fever and marked prostration. The mortality is high and this form of the disease may terminate by death in one to three weeks.

Since there are no pathognomonic signs or symptoms of this disease, diagnosis rests primarily upon bacteriologic or serologic studies. The simplest procedure is the skin test in which 0.1 c.c. of protein nucleate fraction, Brucellergen, is injected intradermally. As with the tuberculin test, however, a positive reaction does not necessarily mean *active* disease since this tests only the person's sensitivity to the infecting agent and may simply reflect an infection of long ago, one which may have been subclinical and thus unrecognized. The same objection applies to the demonstration of serum agglutinins. With this test, however, there is the advantage that after a week or so the agglutination titer can be again determined. If it is significantly higher the second time, this indicates active disease. Many cases of brucellosis have no demonstrable serum agglutinins. The opsonocytophagic index is very difficult to perform properly and is not suited to routine use. The surest laboratory finding upon which to base a diagnosis of brucellosis is demonstration of the organism in the blood, urine, or feces. This is a dangerous, difficult, and time-consuming procedure. Although the cultures may exhibit growth after a week, one cannot properly consider them to be negative until three or four weeks have elapsed. Furthermore, repeated samplings of the blood may be necessary before the organisms are demonstrated. Since the guinea pig is quite susceptible to these organisms, subcutaneous or intraperitoneal injection of the material in question may substitute for *in vitro* culture. This requires a period of six weeks or so for the disease to develop in unmistakable form.

Brucellosis is a septicemic disease and focal lesions may occur in almost any organ or tissue producing meningitis, osteomyelitis, orchitis, vegetative endocarditis, empyema, etc. There have been relatively few opportunities for thorough postmortem study. The disease affects primarily the reticulo-endothelial system. The spleen is often considerably enlarged, and splenomegaly is a characteristic physical finding. There may be hepatomegaly also, and lymph nodes, particularly those of the mesentery, are usually considerably enlarged, soft, and diffuent. Microscopically, in addition to hyperplasia, there are focal necroses and nodular granulomas which somewhat resemble tubercles. Most epithelial tissues show parenchymatous degeneration.

Tularemia (Rabbit Fever)

Tularemia represents a relatively new disease entity. McCoy and Chapin of the United States Public Health Service first identified the causa-

tive organism in 1911 and named it *tularensis* after Tulare County, California. Very shortly after this Wherry recognized, and for the first time proved, infection in a human being. The bulk of our knowledge and understanding of this disease we owe to the long and efficient work of Edward Francis. Tularemia is caused by *Pasteurella tularensis*, a small gram-negative bacillus which is very pleomorphic, sometimes appearing in coccoid form. It grows only on special culture media. The only other disease caused by a member of the genus *Pasteurella* is plague, and tularemia has much in common with this disease. A variety of wild animals form a natural reservoir for this organism. Especially important in the infection of man are wild rabbits (cottontail), hares (jack rabbit), and ground squirrel. The disease is rapidly fatal

cooked meat of infected animals has produced the disease also. In at least one instance a small epidemic of tularemia occurred from drinking contaminated water.

"A mortality of nearly 4 per cent, a slow convalescence in many cases, and the occurrence of suppurative or granulomatous late lesions with attendant prostration and debility, emphasize the seriousness to the individual of contracting this infection" (Francis). The incubation period is ordinarily three to five days, following which there suddenly develops a headache, chill, and high fever, along with generalized aching and the severe prostration characteristic of *septicemia*. Not until thirty-six to forty-eight hours after this does the patient usually notice painful swollen lymph nodes, most often in an axilla. This may direct his atten-

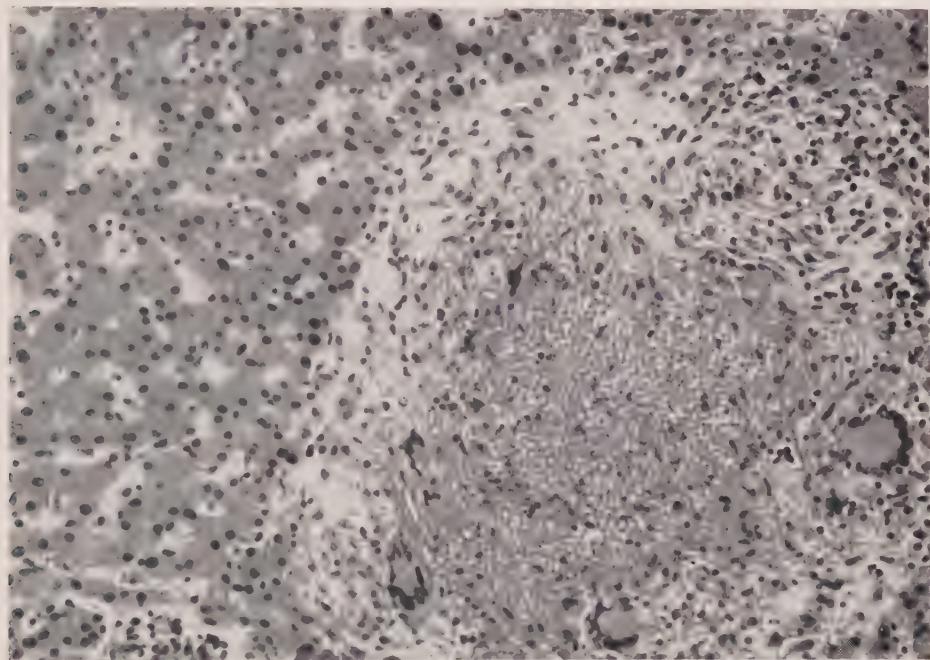


Fig. 153.—Tularemia. The granulomatous reaction in the liver very closely simulates tuberculosis.

in these animals. Francis has estimated that 1 per cent of wild rabbits are infected. In Russia, outbreaks of the disease have occurred in those who obtain and prepare the skins of water rats for the fur industry. Infection will occur from direct contact with infected animals and thus the disease is especially liable to occur in trappers, hunters, butchers, and laboratory workers. *Past. tularensis* is capable of passing readily through the unbroken skin and it is said to be the most dangerous of all infectious agents from the standpoint of the laboratory worker. The second most common method of infection is by the bite of insects, especially ticks (*Dermacentor andersoni*, *D. variabilis*, and *D. occidentalis*) horseflies, or the deer fly (*Chrysops discalis*). Ingestion of the poorly

tion for the first time to the focus of primary infection, an area drained by the involved lymph nodes. Usually this lesion is on the finger or hand. It begins as a tender red papule. Soon there is central necrosis and a "punched-out" ulcer develops. Over three-fourths of the cases are associated with such a primary ulcerating lesion. This is slow to heal and persists, on the average, a month or so. Regional lymph nodes enlarge to a marked degree and resemble somewhat the *buboës* of plague. These enlarged lymph nodes suppurate in about one-fourth of the cases, as a result of which the lymph node may spontaneously rupture and drain cheesy, purulent material. This is the so-called *ulceroglandular type* of the disease and approximately 75 per cent of cases fall within this category. Next in frequency,

accounting for 10 per cent or less of cases, is the *oculoglandular type*, essentially similar to that just described except that the focus of inoculation is the conjunctiva. There is edema, marked hyperemia, itching, and pain. Multiple, small, discrete, yellowish nodules may be seen on the mucous membrane. This is accompanied by cervical lymphadenopathy. Corneal scarring and blindness are occasional sequellae. Less common are the *glandular* and *typhoidal forms* in which there is no evident site of initial infection. Tularemia is a septicemic disease and signs and symptoms often point to a variety of organs. Involvement of the lung, when it occurs, is usually quite evident clinically. Pulmonic lesions may be discrete and nodular, closely resembling tuberculosis, or they may occur in the form of confluent bronchopneumonia or lobar pneumonia. Pneumonia is evident only in the more serious cases and here the mortality is much higher.

Morphologic changes are essentially similar, regardless of which of the four *clinical forms* the disease has taken. Often there is a close resemblance to miliary tuberculosis, and minute, 2 to 3 mm., hard "tubercles" may be found in the liver, spleen, kidneys, lungs, and other organs. If the *tularemic nodules* are of larger size, central necrosis is quite evident and the lesions may be mistaken for abscesses. Tissue changes depend largely upon the stage of the disease. Early in its course the predominant change is focal necrosis. If there has been time for reaction to this, the granulomatous nature of the disease is readily evident. The predominant cell of reaction is the macrophage and these are often arranged in a radial manner around a central area of caseous necrosis, the whole encapsulated in a fibrous capsule. Occasional giant cells of the Langhans' type are seen. Organisms cannot be demonstrated in histologic preparations of human tissues. In addition there is generalized hyperplasia of the reticuloendothelial system. The spleen may be enlarged to 400 to 500 grams and is often palpable upon physical examination. Parenchymatous degeneration is found in many organs.

Sensitivity to bacterial proteins is a prominent feature of tularemia and a small percentage of patients have spectacular cutaneous eruptions during the second or third week. The Foshay intradermal test is very useful in establishing the diagnosis as is also the demonstration of specific agglutinins. A disadvantage of this latter test is that the disease must be a week or so old before antibodies can be demonstrated in the blood. Cross agglutination occurs between *P. tularensis* and brucella organisms so that if either disease is suspected, agglutination titers should be determined against both; the specific titer will be much higher than the other. The organism may be cultured from the local external lesion, from the blood, or, in cases of tularemic pneumonia, from the sputum. In the absence of special media, a guinea pig may be injected and will die of the disease within five to seven days. Although the handling of infected patients is apparently without much hazard, anyone who attempts to culture the organisms is in serious danger of contracting the disease.

Plague (Bubonic Plague, Black Death, Pest)

This most dreaded of medieval diseases has ravaged Europe and Asia in numerous pandemics. One of the most serious of these began in China in 1374, killing 13 million people there, and spreading to involve all of Europe. An estimated 25 million lives were lost to the disease within a three-year period, approximately one-quarter of the total population of Europe at that time. There have been recent pandemics too, the most serious of which raged intermittently for thirty years, affecting principally India, and costing 12 million lives there.

The causative organism is *Pasteurella pestis*, a very pleomorphic, gram-negative coccobacillus which presents bipolar bodies; it is often encapsulated. Depending upon the animal reservoir, two forms of the disease are recognized. Murine plague is that in which rats serve as the primary source of infection. The gray sewer rat is most commonly affected, but as this animal succumbs to the disease he often enters some human dwelling to die. Infected fleas leave his body and an acceptable host is found in the common black house rat. Sylvatic plague is that in which rodents of nondomestic habits are the source of infection. In this country the ground squirrel is most dangerous, but infection has been reported in at least seventy-two different animal species. The disease is endemic in India, China, East Africa, and South America. In this country, an endemic focus of wild rodent plague exists and several outbreaks of human plague have been reported. In 1907-1908, within a twelve-month period, thirty-seven deaths from plague occurred in the San Francisco Oakland area (Holmes) and there have been cases in New Orleans, Beaumont, Galveston, Pensacola; infections have been reported also in southwestern Oregon, Idaho, Utah, and Nevada (Hoekenga). The disease is transmitted to man in two principal ways. Most commonly infection results from the bite of an infected flea (especially *Xenopsylla cheopsis* and *Pulex irritans*). The body louse and bedbug may also serve as means of infection. The pneumonic form of the disease is spread directly from person to person by droplets. Occasionally, there may be direct infection of wounds or other lesions. The incubation period averages two to four days. Although there may be prodromal symptoms of malaise, headache, etc., more often the individual first responds with a sudden chill, fever, and other symptoms of marked toxemia or septicemia, including nausea and vomiting. As in the case of tularemia, it may be a day or two before onset of the very marked lymphadenitis. This occurs most commonly in the inguinal lymph nodes, less often axillary lymph nodes are affected, and only occasionally does it involve cervical lymph nodes. These *buboës* (bubonic plague) are very painful and may attain great size, up to 4 or 5 cm. Profound systemic symptoms continue in this septicemic disease and the patient, first very nervous and apprehensive, may sink into coma and die within a few days. A striking characteristic is the tendency to hemorrhage, first petechial, then purpuric; these spread and may form very large confluent areas so that

the term *black death* is truly descriptive. There are three clinical forms of the disease. That just described represents the *bubonic type* and it is the most common. Death occurs in 60 to 90 per cent of these cases. In the *septicemic form*, there may or may not be buboes. This form of the disease is almost always quickly fatal, as is also the case with the highly infectious *pneumonic form*, in which death may occur within a few hours after first symptoms. A very much milder disease is occasionally seen and this is termed *Pestis minor*. Here the organisms remain localized and septicemia does not occur.

Morphologic changes in those dying from plague represent the effects of overwhelming infection by bacteria which produce potent necrotizing toxins. The picture is everywhere much the same. Large areas of necrotic tissue are seen and these tissues are teeming with organisms. There is relatively little inflammatory exudate present, but much hemorrhage. This is particularly striking in the lungs in the pneumonic form of the disease. In involved lymph nodes (bubo), the gland is almost replaced by hemorrhagic necrotic tissue. This reaction spreads beyond the confines of the capsule and, in the surrounding tissues, necrosis, hemorrhage, and cellulitis are also evident.

animal will die within three to five days, presenting typical findings. Blood cultures are positive in approximately 50 per cent of cases. Extreme caution must be taken in all such procedures, and with the infected person himself, in order that direct infection of man, or an insect vector, may not occur. Streptomycin and sulfadiazine are both somewhat effective in early cases. Active immunization provides but relative temporary protection.

Anthrax

The disease has been known since antiquity, being described in Homer's *Iliad*. It is of great historical interest for it was the first human disease of proved bacterial origin. Although numerous large rod-shaped organisms had been observed in the blood of animals dying from anthrax in 1850, it remained for Robert Koch to prove that this organism was actually the cause of anthrax. This he did in 1876, at the same time formulating what we now accept as Koch's postulates. In 1881 Pasteur succeeded in attenuating the organism and produced an effective vaccine, the first successful practical application of active immunization in the control of disease.

Bacillus anthracis is a long square-ended gram-positive rod which often grows in short chains.



Fig. 154.—Plague. In this lymph node (bubo) observe the extensive area of necrosis and the hemorrhage which has occurred in the surrounding adipose tissue. There is practically no exudative reaction.

The disease may simulate tularemia but its course is so fulminating that its true nature is usually soon evident. Smears may be made from contents of buboes and will usually reveal *Past. pestis* in great numbers. The organisms may be cultured, or an animal (guinea pig or white rat) inoculated. This latter is accomplished by rubbing some of the infected material into the shaved skin of the anterior abdominal wall. If the material contains *Past. pestis*, the

It is capable of forming very resistant spores, but spore forms do not occur in animals or human beings suffering from the disease. A great variety of animals are susceptible to infection, but grazing animals are most commonly affected, especially sheep and cattle. The disease in animals almost invariably results in septicemia and death. In the so-called apoplectic form, death may occur within an hour or two after symptoms are first noticed. Animals, in contrast

to human beings, usually become infected by ingesting the spores. These pass unharmed through the stomach and invade the intestinal mucosa. The spore forms are so resistant that pastures once seeded with *B. anthracis* remain a source of infection indefinitely.

The disease is uncommon in this country (640 cases reported in the United States from 1919 to 1938). Among human beings it occurs chiefly in those whose occupation brings them into immediate contact with wool, hair, or hides. Farmers, butchers, and veterinarians are occasionally infected and a small number of cases have been reported in which the disease followed the use of a shaving brush or hair brush containing contaminated bristles. Infection also occurs from biting flies (family, *Tabanidae*). Most commonly the disease occurs in the form of the malignant pustule, as a result of entry of *B. anthracis* into an abrasion or scratch of the skin. In the majority of instances the primary infection is of the head or neck. The lesion first appears as a pimple, soon surrounded by a zone of edema and hyperemia. Vesiculation occurs and, upon rupture of the small blister, an eschar forms. Soon there is central necrosis and a small ragged black ulcer develops. This may be surrounded by minute vesicles or pustules. Sometimes the local lesion involves a large area. The lesion is not particularly painful although characteristically there is intense itching. Regional lymph nodes are somewhat swollen and tender, but involvement is not comparable to that seen in tularemia or plague. In the majority of instances the disease remains localized and, in a week or two, the small ulcer heals. The eschar may separate from the underlying tissue leaving a suppurating slough. Especially if lymphadenopathy is a prominent feature, forces of localization may be overcome and septicemia result. This is accompanied by profound systemic manifestations and death is the usual consequence. Occasionally no ulcer forms at the site of initial infection, but rather an area of malignant edema. This may or may not be associated with acute hyperemia and other signs of acute inflammation. Generalization of the infection, i.e., septicemia, is more likely to occur here than in the case of the malignant pustule. Next in frequency is the pneumonic form (woolsorter's disease) which occurs from inhalation of the spores. In this case the malignant pustule forms in a bronchus and this soon leads to an extensive bronchopneumonia. There are marked systemic manifestations, progressive dyspnea, and cough productive of bloody sputum. Septicemia and death occurs in the great majority of those affected. Rarely in human beings there occurs a form quite similar to that which is seen in cattle, namely, the intestinal type. Here, too, septicemia and death usually results.

Morphologic changes are characterized principally by a bloody gelatinous edema which affects many tissues and which is found in most serous cavities. Meningitis may be a prominent feature. The damage wrought by *B. anthracis* in the septicemic form is so overwhelming that there is relatively little cellular reaction, principally necrosis with massive bloody edema. In the acute septicemic forms of anthrax,

death occurs in over 90 per cent of the cases unless treated promptly with specific antiserum or penicillin.

In cases with typical skin manifestations, the diagnosis is not difficult. Large numbers of the characteristic organisms can be seen in smears made from the "pustule," or from sputum in the pulmonic form. The organisms should also be cultured and their virulence ascertained by inoculation into guinea pigs or mice.

Glanders and Melioidosis

Glanders is another example of a disease which affects animals primarily; man is but rarely involved and then, it would seem, by accident. This is a disease of horses and mules principally, and in these animals may assume either of two forms: *Glanders* is a relatively acute disease affecting principally the lungs and bringing death, in the majority of cases, within four to six weeks. *Farcy* is a relatively chronic condition which involves primarily the skin, subcutaneous tissues, and lymphatic vessels there. The disease is caused by *Malleomyces mallei* (*Pfeifferella*), a rather pleomorphic, usually slender gram-negative rod. It does not produce an exotoxin. The disease is uncommon in human beings and almost confined to those who work closely with horses and mules, or with laboratory workers who cultivate the organism, hence its incidence has dropped sharply in recent years. This organism ranks with *Bact. tularensis* in the hazard which it presents to the laboratory worker. Although this organism can penetrate intact epithelium, the site of infection is usually an abrasion or other minor injury to the skin, following which there develops a small nodule which usually ulcerates. Regional lymph nodes become swollen and tender. Shortly thereafter fever, and frequently a mucopurulent nasal discharge occurs. An important characteristic at this stage of the process is the very marked prostration, disproportionate to other signs and symptoms. Many patients develop a generalized pustular rash involving skin and mucous membranes, not unlike that of smallpox. Focal areas of suppuration or nodular granulomas occur in many organs, the joints, and especially in the subcutaneous tissues (fancy buds) where they ulcerate and discharge a thick, tenacious, bloody pus.

Morphologically, the disease resembles pyemia, with abscesses to be found in many organs. Often, if the disease is chronic, granulomatous reaction may predominate. It is particularly this chronic form that may simulate other infectious diseases and this condition may persist, with frequent remissions, for years. Formerly, the disease in its acute form was almost always fatal; in the chronic form, mortality was 50 to 70 per cent; streptomycin has reduced this figure.

Diagnosis rests upon demonstration of complement fixing antibodies or recovery of the organism from a subcutaneous lesion, preferably a recent one, or guinea pig inoculation (Straus reaction). Skin tests (mallein) become positive in three to four weeks and resemble a positive tuberculin test.

Melioidosis is comparable to glanders save that rodents are the animal reservoir. The causative organism is *B. whitmori*. Relatively few cases are reported in the world literature. The disease is almost invariably fatal. Morphologic changes are similar to those described for glanders.

Pertussis (Whooping Cough)

From the standpoint of mortality and morbidity this is the most important acute infectious disease of early childhood. It is responsible for more deaths among children under 2 years old than any other communicable disease. Approximately 90 per cent of cases occur during the first five years of life and at least 50 per cent before the age of 2 years. It is during this early period (first two years) that mortality is excessive, from 20 to 36 per cent as a rule. Pertussis is caused by *Hemophilus pertussis* (*Bordet-Gengou bacillus*) a short gram-negative bacillus which closely resembles *H. influenzae*.

tressing cough which has earned the common name of whooping cough. A paroxysm of short violent coughs, perhaps as many as twenty, is followed by a long drawn inspiratory gasp or whoop and this in turn is usually followed by vomiting. When there is premonitory warning, the child becomes very apprehensive and seeks every means, but unsuccessfully, to avoid this harrowing and exhausting experience. The violent force of the cough is apparent from the livid face and protruding eyes. It is manifest also in the pulmonary emphysema (microscopic) which almost invariably occurs. In addition, hemorrhages may result, especially of the conjunctiva and occasionally of the brain. Intestinal hernia and, rarely, prolapse of the rectum have occurred as a result of these paroxysms. The third stage of the disease is one of decline or convalescence and this lasts from one to three weeks. All in all, the disease often requires two months to run its course. The most serious complication, and one which is responsible for the majority of deaths, is secondary bronchopneu-

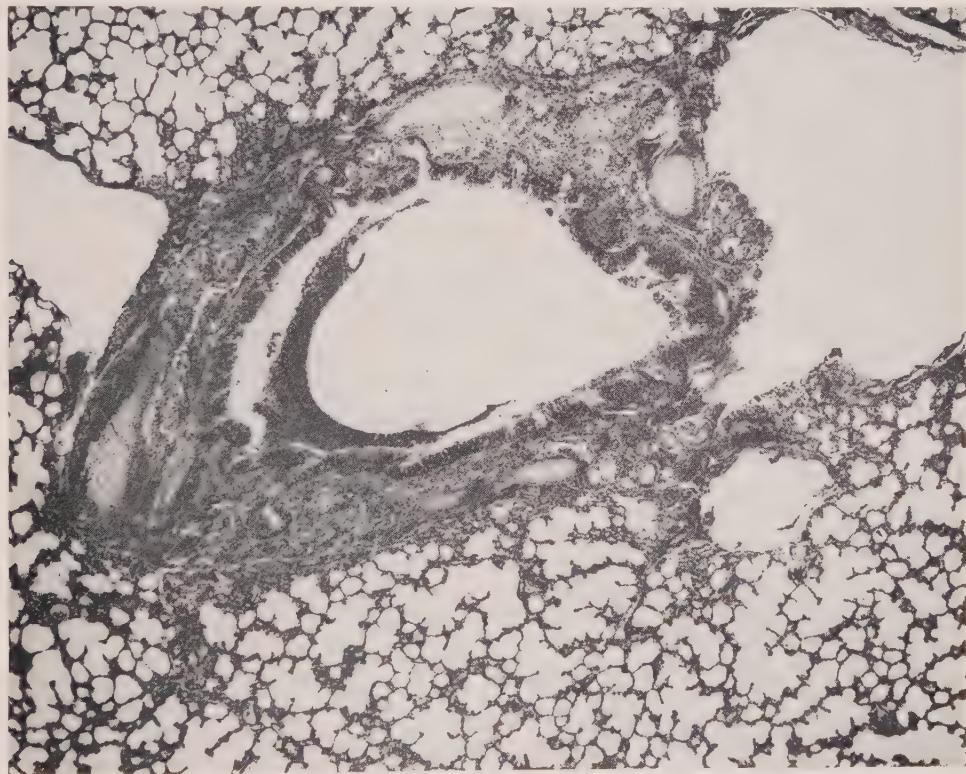


Fig. 155.—Pertussis. Observe the tenacious exudate which clings to the side of the bronchus. There is bronchitis and peribronchitis and, in addition, focal areas of emphysema.

The incubation period is ordinarily from one to two weeks and first manifestations of the disease may suggest an ordinary cold. This is termed the *catarrhal stage* and lasts a week or two. With the onset of characteristic cough, the *paroxysmal stage* is entered and this usually persists for two to four weeks. It is the peculiar and very dis-

monia. The organisms most often responsible for this are *H. influenzae* and *Str. pyogenes*. Second in importance is the complication of *cerebral hemorrhage*. This may result in death, hemiplegia, or other permanent neurological changes. Convulsions are frequently observed, especially in infants with a severe form of the disease. These

have been variously explained on the basis of: a neurogenic toxin, cerebral anoxia, cerebral hemorrhage, alkalosis, acidosis, and hypocalcemia.

Occasionally, one encounters an abortive form of the disease in which cough is not accompanied by a characteristic whoop. Cough plates prepared within the first two or three weeks of the disease, will demonstrate the specific organism in 80 to 90 per cent of cases. After this time *H. pertussis* cannot ordinarily be recovered, but complement fixing antibodies will have appeared in the blood. The blood count is rather characteristic in that leukocytosis is usually marked, averaging 30,000 or so, with the majority of cells being lymphocytes (60 to 70 per cent). Not infrequently leukemoid reactions occur in which the white blood cell count may exceed 100,000.

Morphologic changes, in the uncomplicated case, are almost limited to the air passages and lungs. There is laryngitis, tracheitis, bronchitis, and bronchiolitis, but changes are most marked in the bronchi. Bacterial stains reveal many of the specific organisms contained within the mucopurulent exudate which overlays the mucosa and intertwined and tangled with the cilia of the columnar epithelium. Occasionally areas of superficial necrosis and erosion are evident. There is hyperemia and excessive production of mucus. Occasional small bronchi contain dense plugs of mucus and these include a few inflammatory cells and many organisms. Peribronchitis and interstitial pneumonitis, especially around small bronchi, are characteristic findings, but by no means pathognomonic since this is seen also in other diseases, e.g., atypical pneumonia. Little exudate is to be found in alveoli unless there is secondary bronchopneumonia. Emphysema is almost always evident microscopically. Peribronchial lymph nodes are hyperemic and exhibit moderate hyperplasia.

References

- Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, 1945, W. B. Saunders Co.
- Berman, J. K.: Principles and Practice of Surgery, St. Louis, 1949, The C. V. Mosby Co.
- Dubos, René J.: Bacterial and Mycotic Infections of Man, Philadelphia, 1948, J. B. Lippincott Co.
- Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., 1935, Charles C. Thomas.
- Holmes, W. H.: Bacillary and Rickettsial Infections, New York, 1940, The Macmillan Co.
- Joe, A.: The Acute Infectious Fevers, Philadelphia, 1947, The Blakiston Co.
- Mackie, T. T., Hunter, G. W., III, and Worth, C. B.: A Manual of Tropical Medicine, Philadelphia, 1945, W. B. Saunders Co.
- Menkin, V.: Dynamics of Inflammation, New York, 1940, The Macmillan Co.
- Pullen, R. L.: Communicable Diseases, Philadelphia, 1950, Lea & Febiger.
- Rolleston, J. D., and Ronaldson, G. W.: Acute Infectious Diseases, ed. 3, St. Louis, 1940, The C. V. Mosby Co.
- Stimson, P. M.: Common Contagious Diseases, ed. 4, Philadelphia, 1947, Lea & Febiger.
- Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunology, ed. 3, Baltimore, 1947, Wm. Wood & Co.

Characteristics of Bacteria and Their Toxins

- Duran-Reynals, F.: Bact. Rev. 6: 197, 1942.
- Eaton, M. D.: Bact. Rev. 2: 3, 1938.
- Lewis, I. M.: Bact. Rev. 5: 181, 1941.
- Macfarlane, M. G., and Knight, B. C. J. G.: Biochem. J. 35: 884, 1941.
- Pappenheimer, A. M., Jr.: Fed. Proc. 6: 479, 1947.
- Schwabacher, H., Cunliffe, A. C., Williams, R. E. O., and Harper, G. J.: Brit. J. Exper. Path. 26: 124, 1945.
- Shwartzman, G., Klempner, P., and Gerber, I. E.: J. A. M. A. 107: 1946, 1936.
- Smith, W., Hale, J. H., and Smith, M. M.: Brit. J. Exper. Path. 28: 57, 1947.
- van Heyningen, W. E.: Bacterial Toxins, Oxford, 1950, Blackwell Scientific Publications.

General Aspects of Reaction to Bacterial Injury

- Cannon, P. R.: Physiol. Rev. 20: 89, 1940.
- Cartwright, G. E.: Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: J. Clin. Investigation 25: 65, 1946.
- Holmes, E.: Physiol. Rev. 19: 439, 1939.
- Mudd, S., and Anderson, T. F.: J. Immunol. 42: 251, 1941.
- Rich, A. R.: Physiol. Rev. 21: 70, 1941.
- Robscheit-Robbins, F. S., and Whipple, G. H.: J. Exper. Med. 63: 767, 1936.

Bacterial Specificity and Localization

- Baxton, R. W., and White, M. L., Jr.: Surgery 13: 309, 1943.
- Blalock, A., and Burwell, C. S.: Surg., Gynec. & Obst. 73: 433, 1941.
- Buchbinder, L.: J. A. M. A. 118: 718, 1942.
- Carmichael, F. A., Kernohan, J. W., and Adams, A. W.: Arch. Neurol. & Psychiat. 42: 1001, 1939.
- Davie, T. B., Lakin, C. E., Love, R. J. M., and Corbet, R. M.: Practitioner 147: 545, 1941.
- Grodinsky, M.: Ann. Surg. 110: 177, 1939.
- McKay, Jack, Edwards, C. E., and Leonard, H. B.: Am. J. Clin. Path. 17: 479, 1947.
- Mudd, S.: Bull. New York Acad. Med. 21: 393, 1945.
- Neuhof, H., and Aufses, A. H.: Surg., Gynec. & Obst. 77: 544, 1943.
- Ochsner, A., DeBakey, M., and Murray, S.: Am. J. Surg. 40: 292, 1938.
- Rhoads, P. S.: Am. Practitioner 1: 305, 1947.
- Sandholzer, L. A., and Scott, W. W.: J. Urol. 42: 183, 1939.
- Steinberg, B.: Infections of the Peritoneum, New York, 1944, Paul B. Hoeber, Inc.

Staphylococcal Infections

- Altemeier, W. A.: Int. Abst. Surg. 75: 518, 1942.
- Baker, R. D.: South. M. J. 35: 240, 1942.
- Beamer, P. R., Goodoff, I. I., and Smith, E. B.: Am. J. Clin. Path. 14: 350, 1944.
- Berger, L.: Valle, A., and Vezins, C.: Arch. Path. 21: 273, 1936.
- Blair, J. E.: Bact. Rev. 3: 97, 1939.
- Fink, A. A.: Arch. Path. 31: 103, 1941.
- Finland, M., Peterson, O. L., and Strauss, E.: Arch. Int. Med. 70: 183, 1942.
- Mendell, T. H.: Arch. Int. Med. 63: 1068, 1939.
- Rigdon, R. H.: Am. J. M. Sc. 199: 412, 1940.
- Skinner, D., and Keever, C. S.: Arch. Int. Med. 68: 851, 1941.
- Wollenman, O. J., Jr., and Finland, M.: Am. J. Path. 19: 23, 1943.
- Williams, R. E. O., and Miles, A. A.: J. Path. & Bact. 57: 27, 1945.
- Zeisler, E. P.: M. Clin. North America 26: 83, 1942.

Streptococcal Infections

- Brody, H., and Smith, L. W.: Am. J. Path. 12: 373, 1936.
- Colebrook, L., and Hare, R.: J. Obst. & Gynaec., Brit. Emp. 40: 609, 1933.
- Commission on Acute Respiratory Diseases: J. A. M. A. 125: 1163, 1944.

57. Commission on Acute Respiratory Diseases: Am. J. Pub. Health **35**: 675, 1945.
 58. Dick, G. F., and Dick, G. H.: Scarlet Fever, Chicago, 1938, Year Book Publishers, Inc.
 59. Evans, A. C., and Chinn, A. L.: J. Bact. **54**: 495, 1947.
 60. Flynn, J. E.: Surg., Gynec. & Obst. **76**: 227, 1943.
 61. Hamburger, M., Jr., Hilles, C. H., Johnson, M. A., and Wallin, J. G.: J. A. M. A. **124**: 564, 1944.
 62. MacLennan, J. D.: Lancet **1**: 582, 1943.
 63. Mallory, G. K., and Keefer, C. S.: Arch. Path. **32**: 334, 1941.
 64. Rantz, L. A., Spink, W. W., and Boisvert, P. J.: Arch. Int. Med. **79**: 272, 1947.
 65. Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Arch. Int. Med. **79**: 401, 1947.
 66. Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Arch. Int. Med. **78**: 369, 1946.
 67. Soloman, S., and Kalkstein, M.: Am. J. M. Sc. **205**: 765, 1943.

Pneumococcic Infections

68. Cecil, R. L., Baldwin, H. S., and Larsen, N. P.: Tr. A. Am. Physicians **41**: 208, 1926.
 69. Feinblatt, H. M.: Boston M. & S. J. **189**: 136, 1923.
 70. Finland, M.: Medicine **21**: 307, 1942.
 71. Heffron, R.: Pneumonia; With Special Reference to Pneumococcus Lobar Pneumonia, New York, 1939, Commonwealth Fund.
 72. Nemir, R. L., Andrews, E. T., and Vinograd, J.: Am. J. Dis. Child. **51**: 1277, 1936.
 73. Robertson, O. H.: Ann. Int. Med. **18**: 1, 1943.
 74. Robertson, O. H., and Hamburger, M.: J. Exper. Med. **72**: 261, 1940.
 75. Robertson, O. H., and Uhley, C. G.: J. Clin. Investigation **15**: 115, 1936.
 76. Wood, W. B., and Irons, E. N.: J. Exper. Med. **84**: 365, 377, 387, 1946.

Meningococcic Infections

77. Adams, F. D.: Ann. Int. Med. **20**: 33, 1944.
 78. Black-Schaffer, B., Hibert, T. C., and Kerby, G. P.: Arch. Path. **48**: 28, 1947.
 79. Branham, S. E.: Bact. Rev. **4**: 59, 1940.
 80. Daniels, W. B., and Jaquette, W. A., Jr.: J. A. M. A. **123**: 1, 1943.
 81. Goldbloom, A. A., Nickman, E. H., and Seidmon, E. P.: Ann. Int. Med. **24**: 589, 1946.
 82. Herbut, P. A., and Mages, W. E.: Arch. Path. **36**: 413, 1943.
 83. Moritz, A. R., and Zamcheck, N.: Arch. Path. **42**: 459, 1946.
 84. Silverthorne, N., and Cameron, C.: J. Pediat. **19**: 618, 1941.
 85. Smith, H. W., Thomas, L., Dingle, J. H., and Finland, M.: Ann. Int. Med. **20**: 12, 1944.
 86. Strong, P. S.: Am. J. M. Sc. **206**: 561, 1943.
 87. Thomas, H. B., and Leiphart, C. D.: J. A. M. A. **125**: 884, 1944.
 88. Thomas, H. M., Jr.: J. A. M. A. **123**: 264, 1943.
 89. Wright, D. O., and Reppert, L. B.: Arch. Int. Med. **77**: 143, 1946.

Gonococcic Infections

90. Branham, S. E., Mitchell, R. H., and Brainin, W.: J. A. M. A. **110**: 1804, 1938.
 91. Campbell, M. F.: Ann. Surg. **86**: 577, 1927.
 92. Mahoney, J. F., Van Slyke, C. J., Cutler, J. C., and Blum, H. L.: Am. J. Syph., Gonor. & Ven. Dis. **30**: 1, 1946.
 93. Miller, C. P., and Hawk, W. D.: Tr. A. Am. Physicians **55**: 216, 1940.
 94. Pelouse, F. S.: Gonorrhea in the Male and Female, revised reprint of ed. 3, Philadelphia, 1943, W. B. Saunders Co.
 95. Rice, J. L., Cohn, A., Steer, A., and Adler, E. L.: J. A. M. A. **117**: 1766, 1941.

Infections With *H. Influenzae*

96. Craven, E. B., Jr., Poston, M. A., and Orgain, E. S.: Am. Heart J. **19**: 434, 1940.
 97. Neal, J. B., Jackson, H. W., and Appelbaum, E.: J. A. M. A. **102**: 513, 1934.

Infections With Bacilli of *Proteus* Group

98. Hirsch, E. F., and Shapiro, D. A.: J. A. M. A. **109**: 937, 1937.
 99. MacKenzie, D. W., and Hawthorne, A. B.: J. Urol. **30**: 277, 1933.
 100. Neter, E., and Chait, R. A.: Arch. Otolaryng. **32**: 946, 1940.
 101. Neter, E. R., and Farrar, R. H.: Am. J. Digest. Dis. **10**: 344, 1943.

Infection With *Ps. Aeruginosa*

102. Epstein, J. W., and Grossman, A. B.: Am. J. Dis. Child. **46**: 132, 1933.
 103. Kline, B. S., and Maschke, A. S.: J. A. M. A. **98**: 528, 1932.
 104. Schaffer, A. J., and Oppenheim, E. H.: South. M. J. **41**: 460, 1948.
 105. Slutsky, N., and Matlin, P.: J. A. M. A. **113**: 1400, 1939.

Infection With *E. Coli*

106. Barrett, G. S., Rammelkamp, C. H., and Worcester, J.: Am. J. Dis. Child. **63**: 41, 1942.
 107. Dubin, I. N., and Kerby, G. P.: Arch. Path. **35**: 808, 1943.
 108. Schaub, I. G.: J. Lab. & Clin. Med. **31**: 958, 1946.

Infection With *K. Pneumoniae*

109. Baehr, G., Schwartzman, G., and Greenspon, E. B.: Ann. Int. Med. **10**: 1788, 1937.
 110. Hyde, L., and Hyde, B.: Am. J. M. Sc. **205**: 660, 1943.
 111. Jaffe, S. A.: J. A. M. A. **122**: 292, 1943.
 112. Julianelle, L. A.: Ann. Int. Med. **15**: 190, 1941.
 113. Profant, H. J.: Ann. Otol., Rhin. & Laryng. **47**: 379, 1938.
 114. Solomon, S.: New England J. Med. **237**: 149, 1947.
 115. Swartz, E. P., and Rohde, P. A.: Am. J. Clin. Path. **16**: 88, 1946.

"Mixed Infections"

116. Black, W. C.: Am. J. Dis. Child. **56**: 126, 1938.
 117. Burrows, W.: Biol. Symposia **8**: 89, 1942.
 118. Field, H., Jr.: J. Clin. Investigation **18**: 707, 1934.
 119. Kelly, F. C.: J. Infect. Dis. **74**: 93, 1944.
 120. Kline, B. S., and Berger, S. S.: Arch. Int. Med. **56**: 753, 1935.

Infection With Nonspore-Forming Anaerobic Bacilli

121. Dock, G. M.: Bact. Rev. **4**: 227, 1940.
 122. Ruys, A. C.: J. Path. & Bact. **59**: 313, 1947.
 123. Smith, W. E., and Rose, M. W.: New England J. Med. **232**: 31, 1945.

Focal Infection

124. Billings, Frank: Focal Infection. The Lane Medical Lectures, New York, 1917, D. Appleton & Co.
 125. Crowley, M. C.: Am. J. Orthodontics, Oral Surg. Sect. **32**: 126, 1946.
 126. Freyberg, R. H.: J. Am. Dent. A. **33**: 1101, 1946.
 127. Haden, R. L.: Dental Infection and Systemic Disease, Philadelphia, 1936, Lea & Febiger.
 128. Reimann, H. A., and Havens, W. B.: J. A. M. A. **114**: 1, 1940.
 129. Rosenow, E. C.: Internat. Clin. **2**: 29, 1930.

Diphtheria

130. Collins, S. D.: Pub. Health Rep. **61**: 203, 1946.
 131. McLeod, J. W.: Bact. Rev. **7**: 1, 1943.
 132. Warthin, A. S.: J. Infect. Dis. **33**: 32, 1924.

Tetanus

133. Abel, J. J., Firor, W. M., and Chalian, W.: Bull. Johns Hopkins Hosp. **63**: 373, 1938.

134. Abel, J. J., Hampil, B., Jonas, A. F., and Chalian, W.: Bull. Johns Hopkins Hosp. **62**: 522, 1938.
 135. Baker, A. B.: Am. J. Path. **19**: 709, 1943.
 136. Francis, E.: U. S. Public Health Service Hygienic Lab. Bull. No. 95, 1914.
 137. Friedemann, U., Hollander, A., and Tarlov, I. M.: J. Immunol. **40**: 325, 1941.
 138. Vener, H. I., and Bower, A. G.: J. A. M. A. **116**: 1627, 1941.
 139. Weinstein, B. B., and Beacham, W. D.: Am. J. Obst. & Gynec. **42**: 1031, 1941.

Gas Gangrene

140. Butler, H. M.: J. Obst. & Gynaec., Brit. Emp. **50**: 105, 1943.
 141. Evans, D. G.: Brit. J. Exper. Path. **28**: 24, 1947.
 142. Govan, A. D. Telford: J. Path. & Bact. **58**: 423, 1946.
 143. Robb-Smith, A. H.: Lancet **2**: 362, 1945.

Food Poisoning

144. Buchbinder, L., Olser, A. G., and Steffen, G. I.: Pub. Health Rep. **63**: 109, 1948.
 145. Dock, G. H.: Food Poisoning, Chicago, 1943, University of Chicago Press.
 146. Mosher, W. E., Jr., Wheeler, S. M., and Chand, H. L.: Pub. Health Rep. **56**: 2415, 1941.

Typhoid and Paratyphoid Fevers

147. Typhoid in the Large Cities of the United States in 1946, "Special Article," J. A. M. A. **134**: 1086, 1947.
 148. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, 1945, W. B. Saunders Co.
 149. Bondy, P. K., and Barnwell, C. H.: J. Urol. **57**: 642, 1947.
 150. Goodpasture, E. W.: Am. J. Path. **18**: 175, 1937.
 151. Stuart, B. M., and Pullen, R. L.: Arch. Int. Med. **78**: 629, 1946.

Bacillary Dysentery

152. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, 1945, W. B. Saunders Co.
 153. Callender, G. R.: Am. J. Trop. Med. **14**: 207, 1934.
 154. Felsen, J.: Bacillary Dysentery, Colitis, and Enteritis, Philadelphia, 1945, W. B. Saunders Co.
 155. Hardy, A. V., and Watts, J.: J. A. M. A. **124**: 1173, 1944.
 156. Macumber, H. H.: Arch. Int. Med. **69**: 624, 1942.
 157. Manson-Bahr, P.: The Dysenteric Disorders, Baltimore, 1939, Williams & Wilkins Co.
 158. Penner, A., and Bernheim, A. I.: J. Exper. Med. **76**: 271, 1942.
 159. Shaughnessy, H. J., Olsson, R. C., Bass, K., Frierer, F., and Levinson, S. O.: J. A. M. A. **132**: 362, 1946.
 160. Thomas, A. R., Jr., and Levine, M.: Am. J. Clin. Path. **16**: 98, 1946.
 161. Van Gelder, D. W., Daines, W. P., and Fischer, G. L.: Am. J. Trop. Med. **27**: 225, 1947.

Cholera

162. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, 1945, W. B. Saunders Co.
 163. Burrows, W., Mather, A. N., Elliott, M. E., and Wagner, S. M.: J. Infect. Dis. **79**: 159, 1946.
 164. Linton, R. W.: Bact. Rev. **4**: 261, 1940.

Brucellosis

165. Carpenter, C. M.: M. Clin. North America **27**: 698, 1943.
 166. Evans, Alice C.: Am. J. Pub. Health **37**: 139, 1947.

167. Foshay, L.: Am. J. Clin. Path. **10**: 176, 1940.
 168. Gould, S. E., and Huddleson, I. F.: J. A. M. A. **109**: 1971, 1937.
 169. Harris, H. J.: Brucellosis, ed. 2, New York, 1950, Paul B. Hoeber, Inc.
 170. Hoffbauer, F. W., and Spink, W. W.: J. Lab. & Clin. Med. **32**: 315, 1947.
 171. Howe, C., Miller, E. S., Kelly, E. H., Bookwalter, H. L., and Ellingson, H. V.: New England J. Med. **236**: 741, 1947.
 172. Huddleson, I. F.: Brucellosis in Man and Animals, rev. ed. New York, 1943, The Commonwealth Fund.
 173. Jordan, C. F., and Borts, I. H.: Am. J. Med. **2**: 156, 1947.
 174. Parsons, P. B., and Poston, M. A.: South. M. J. **32**: 7, 1939.
 175. Ruiz-Castaneda, M.: Proc. Soc. Exper. Biol. & Med. **64**: 298, 1947.
 176. Sharp, W. B.: Arch. Path. **18**: 72, 1934.
 177. Sundberg, R. D., and Spink, W. W.: Blood, Supp. **1**: 7, 1947.
 178. Brucellosis, A Symposium, Am. Assoc. for Adv. of Sc., Washington, 1950.

Tularemia

179. Francis, E., and Callendar, G. R.: Arch. Path. **3**: 577, 1937.
 180. Goodpasture, E. W., and House, S. J.: Am. J. Path. **4**: 213, 1928.
 181. Hunt, J. S.: Ann. Int. Med. **26**: 263, 1947.
 182. Lillie, R. D., Francis, E., and Parker, R. R.: Bull. Nat. Inst. Health, No. 16, 1936.
 183. Pullen, R. L., and Stuart, B. M.: J. A. M. A. **129**: 495, 1945.
 184. Simpson, W. M.: Tularemia, New York, 1929, Paul B. Hoeber, Inc.
 185. Stuart, B. M., and Pullen, R. L.: Am. J. M. Sc. **210**: 223, 1945.

Plague

186. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, 1945, W. B. Saunders Co.
 187. Hampton, B. C.: Pub. Health Rep. **55**: 1143, 1940.
 188. Hoekenga, M. T.: J. Trop. Med. **50**: 190, 1947.
 189. Meyer, K. F.: Am. J. Trop. Med. **22**: 9, 1942.
 190. Meyer, K. F.: Ann. New York Acad. Sc. **48**: 429, 1946.
 191. Ruegsegger, J. M., and Gilchrist, H.: Am. J. Trop. Med. **27**: 683, 1947.
 192. Meyer, K. F.: M. Clin. North America, p. 745, May, 1943.

Anthrax

193. Bloom, W. L., McGhee, W. J., Cromartie, W. J., and Watson, D. W.: J. Infect. Dis. **80**: 137, 1947.
 194. Cowdry, J. S.: Arch. Path. **43**: 396, 1947.
 195. Cromartie, W. J., Bloom, W. L., and Watson, D. W.: J. Infect. Dis. **80**: 1, 1947.
 196. Cromartie, W. J., Watson, D. W., Bloom, W. L., and Heckly, R. J.: J. Infect. Dis. **80**: 14, 1947.
 197. Ellingson, H. V., Kadull, P. J., Bookwalter, H. L., and Howe, C.: J. A. M. A. **131**: 1105, 1946.
 198. Eurich, F. W.: Brit. M. J. **2**: 50, 1933.
 199. Gold, H.: Arch. Int. Med. **70**: 785, 1942.
 200. Lebowich, R. J., McKillip, B. G., and Conboy, J. R.: Am. J. Clin. Path. **13**: 505, 1943.
 201. Smyth, H. F., and Higgins, W. D.: Am. J. Pub. Health **35**: 850, 1945.

Glanders and Melioidosis

202. Beamer, P. R., Varney, P. L., Brown, W. G., McDowell, F., and Eck, B.: Am. J. Path. **24**: 717, 1948.
 203. Bernstein, J. M., and Carling, E. R.: Brit. M. J. **1**: 319, 1909.
 204. Cox, C. D., and Arbogast, J. L.: Am. J. Clin. Path. **15**: 567, 1945.
 205. Howe, C., and Miller, W. R.: Ann. Int. Med. **26**: 93, 1947.

Pertussis

206. Proom, H.: *J. Path. & Bact.* **50**: 165, 1947.
 207. Saur, L. W., in Brennemann, J.: *Practice of Pediatrics*, vol. 2, chap. 34, Hagerstown, Md., 1944, W. F. Prior Co.
 208. Smith, L. W.: *Arch. Path.* **4**: 732, 1927.

Chancroid

209. Greenwald, E.: *J. A. M. A.* **121**: 9, 1943.
 210. Heyman, A., Beeson, P. B., and Sheldon, W. H.: *J. A. M. A.* **129**: 935, 1945.
 211. Sheldon, W. H., and Heyman, A.: *Am. J. Path.* **22**: 415, 1946.
 212. Sullivan, M.: *Am. J. Syph.* **24**: 482, 1940.

Erysipeloid

213. Barber, M.: *J. Path. & Bact.* **48**: 11, 1939.
 214. Barber, M., Nellen, M., and Zoob, M.: *Lancet* **1**: 125, 1946.
 215. Julianelle, L. A.: *J. Bact.* **42**: 385, 1941.
 216. Klauder, J. V.: *J. A. M. A.* **111**: 1345, 1948.

Ratbite Fever

217. Allbritten, F. F., Sheely, R. F., and Jeffers, W. A.: *J. A. M. A.* **114**: 2360, 1940.
 218. Borgen, L. O.: *Acta path. et microbiol. Scandinav.* **25**: 161, 1948.
 219. Brown, T. McP., and Nuncemaker, J. C.: *Bull. Johns Hopkins Hosp.* **70**: 201, 1942.
 220. Kirkwood, T., and Stall, C. G.: *Illinois M. J.* **80**: 141, 1941.

221. Larson, C. L.: *Pub. Health Rep.* **56**: 1961, 1941.
 222. Richter, C. P.: *J. A. M. A.* **128**: 324, 1945.
 223. Rountree, P. M., and Rohan, M.: *M. J. Australia* **1**: 359, 1941.
 224. Sprecher, M. H., and Copeland, J. R.: *J. A. M. A.* **134**: 1014, 1947.

Human and Animal Bites

225. Boyce, F. F.: *South. M. J.* **35**: 631, 1942.
 226. Levin, I. A., and Longacre, A. B.: *J. A. M. A.* **147**: 815, 1951.
 227. Mason, M. L., and Kock, S. L.: *Surg., Gynec. & Obst.* **51**: 591, 1930.
 228. Neter, E.: *Proc. New York State Assoc. Pub. Health Lab.* **31**: No. 1, p. 6.

Miscellaneous

229. Burn, C. G.: *Am. J. Path.* **12**: 341, 1936.
 230. Julianelle, L. A.: *Ann. Int. Med.* **14**: 608, 1940.
 231. Leach, J. E., and Medinger, F. G.: *Ann. Int. Med.* **15**: 609, 1941.
 232. Murray, E. G. D., Webb, R. A., and Swann, M. B. R.: *J. Path. & Bact.* **29**: 407, 1926.
 233. Rantz, L. A., and Kirby, W. M. M.: *Arch. Int. Med.* **31**: 516, 1943.
 234. Reimann, H. A.: *J. Clin. Investigation* **14**: 311, 1935.
 235. Sabin, A. R.: *Bact. Rev.* **5**: 1, 1941.
 236. Schatlenbarg, H. J., and Harris, W. H.: *J. A. M. A.* **117**: 2069, 1941.
 237. Seastone, C. V.: *J. Exper. Med.* **62**: 203, 1935.

Chapter 11

TUBERCULOSIS

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Historical Note.—Tuberculosis was proved to be a specific infectious disease by the animal experiments of Villemin (1865) several years before the causative bacillus was isolated in cultures and identified in stained smears. Interest in the possibilities of specific immunity in tuberculous infection was greatly stimulated by the investigations of Koch (1882). In 1793, Matthew Baillie described the gross appearance of tubercles at various stages of their development. Bayle (1810) made important contributions to the morphology of tuberculosis, and one of Bayle's students, Laennec, was inspired to further studies in this field, extending the studies of Bayle, Bichat, and others, besides his other important contributions to pathology and clinical medicine. All three of these men died of tuberculosis.¹ The anatomical relationships between lesions in the pulmonary parenchyma and those in the related lymph nodes became known gradually by the studies of pathologists and clinicians over a period of many years and the published work includes the now famous names of Parrot (1876), Küss (1898), E. Albrecht (1907), H. Albrecht (1909), and Ghon (1912), to mention only a few of the earlier ones.

Incidence.—Prior to 1800, tuberculosis killed as much as one-fifth of the population, according to estimates made by Long.² Since that time the death rate has continuously declined, reaching a yearly rate of about 200 per 100,000 by 1900 and less than 25 fifty years later³ in the registration area of the United States. However, it still ranks high among the most important causes of death and is considered to be the most important single cause of economic loss due to disease because of the prolonged disability imposed upon its victims. In the age period between 15 and 45, it is responsible for more deaths than any other single cause. The reduction in death rate during recent years has affected the age group between 15 and 24 years most favorably while in those past 65 the rate is slightly on the increase.⁴ In spite of the decline in number of deaths as indicated by death certificate statistics, the reported morbidity rate during approximately the same period showed a striking increase (22 per cent between 1940 and 1947).⁵ The remarkable improvement in death rate has been attributed to a general elevation in standards of living, to improved public health measures, and, in the United States, to the elimination of tuberculosis in cattle. The last is related more particularly to the elimination of abdominal and cervical tuberculosis in children. Besides these factors,

there is an important unexplained factor operating to diminish the virulence of tuberculous infections, possibly comparable with that causing decline in severity of syphilis during the past few centuries. It has been suggested but not proved that the population as a whole is becoming more resistant by the mechanism of gradual elimination of those members most susceptible to the disease. This theory is not acceptable to most students of the subject because of the comparatively short period of time involved.

THE TUBERCLE BACILLUS

Forms and Types.—The mycobacterium of tuberculosis is the most common of the group of acid-fast bacteria which infect man. Its role as the exciting agent of tuberculous infection is not questioned, although there is some dispute regarding the significance of the forms in which it may appear in infected tissues and in artificial cultures. It is commonly admitted that it may assume granular and nonacid-fast forms (Möch's granules) as degeneration phenomena or as phases of growth. Of the types of tubercle bacilli which are known to produce disease in man, there are two main sources, man himself and cattle. Of these, the human source is by far the more important. Except in those areas where tuberculosis of dairy cattle is especially prevalent, practically all tubercle bacilli which have been recovered from pulmonary lesions in human infections are of the human type. An exception to this is found in the high incidence of bovine infections in Scotland where almost one-third of fatal infections at all ages and as many as 3.8 per cent of cases of active pulmonary tuberculosis have been found to be due to bacilli of bovine type.⁶ In the United States, only the rare cases of primary intestinal tuberculosis and of the extremely uncommon primary infections of tonsils with cervical lymphadenopathy (serofulua) can be said usually to be due to bovine infections.

Even as early as 1910, Park and Krumwiede⁷ found that bacilli of bovine type caused less than 10 per cent of infections in children. In their series and in all cases compiled by them, the majority of cases of abdominal (primary intestinal) tuberculosis was caused by bovine-type bacilli. Cervical tuberculosis in children under 5 years was caused by bovine bacilli in 61 per cent, and in those over 5 years, in 38 per cent of cases. Tuberculosis of bones and joints in adults 16 years old and over was due to

bovine infections in 3.3 per cent, in children of 5 to 16, 6.8 per cent, and under 5 years of age, none. The present incidence of infections caused by bovine type bacilli is very much less than indicated by these figures.

With few exceptions, bovine strains are more virulent than human strains for man and laboratory animals. The differentiation of the two types is based upon their relative virulence for rabbits. Freshly isolated bovine strains have the ability to produce progressive lesions in the more resistant as well as the more susceptible laboratory animals, while strains of human type usually are incapable of causing progressive disease in the more resistant species such as cattle, rabbits, dogs, cats, and rats unless very large doses are used for injection. There is some evidence that bovine-type bacilli are also more virulent for human subjects than are human-type strains, but the factor of dosage is so completely an unknown quantity that the evidence is inconclusive. For example, in Park and Krumwiede's series⁷ the mortality for bovine infections was 26 per cent in the age group between 5 and 15 years of age, the group in which the death rate for human-type infections is extremely low. No serologic differences between human and bovine strains are demonstrable. Tuberculous infections due to bacilli of avian type have been reported occasionally but no case occurring in this country has been accepted as satisfactorily proved.⁸

Growth Requirements.—The minimal requirements for growth of tubercle bacilli are relatively simple since they can synthesize most of the necessary compounds which make up their complex structure from much simpler ones. After adaptation to artificial media, even virulent strains may grow indefinitely, and maintain some of their ability to infect animals in media composed of pure chemical substances. For example, the synthetic medium of Proskauer and Beck and that of Long contain only asparagine and ammonium salts as sources of nitrogen, and glycerol as the chief source of carbon. Besides these, hydrogen, phosphorus, potassium, and magnesium are essential for survival and growth. Sulfur, iron, sodium, chlorine, citrates, and other salts promote growth but are not included in the basic requirements.⁹

Cultures which have been recently isolated from animal tissues usually grow poorly or not at all in the synthetic mediums which contain the "basic" substances and require the addition of egg yolk, cream, serum, or other complex substance as a supplement for first growth.

Tubercle bacilli are obligate aerobes and severe restriction of their oxygen supply by exclusion of air will cause slowing or cessation of growth. This fact appears to be the chief basis for success in collapse therapy. When the bacilli in the lung are deprived of oxygen by the artificial collapse of cavities or by obstruction of the bronchi leading to cavities, their growth rate is slowed, thereby tipping the balance in favor of the defense mechanisms of the tissues.

Chemical Structure.—The composition of tubercle bacilli is such that they are destroyed very slowly by phagocytic cells. This property

is usually attributed to the indigestibility of the waxlike constituent of the lipid fraction, but it should not be overlooked that the weak enzymes of the large mononuclear cells which are principally responsible for destroying tubercle bacilli may be inhibited by other constituents of the bacteria. There are complex proteins which act as potent poisons, especially to cells which have been "sensitized" to them, and these may constitute an important factor in inhibiting the destruction of ingested tubercle bacilli by devitalizing or killing outright the cells which contain them. Furthermore, chemical analysis of bacillary masses has yielded carbohydrates, principally polysaccharides. The analytical work of R. J. Anderson,¹⁰ Heidelberger and Menzel,¹¹ Long and Seibert,¹² and others has given us an insight into the chemical constitution of some of the virulent strains of tubercle bacilli. By utilization of these fractions in biologic tests, Sabin¹³ and others have been able to reproduce in the tissues of animals all of the histologic changes which are known to occur in tuberculous infections. So far, none of the fractions has been found to bring about any change in the immune state of the animal, but a state of hypersensitivity can be induced by the injection of antigenic tuberculoprotein.¹⁴ The results of these experiments are interesting but must be interpreted with caution for it is not certain that the fractions obtained from killed cultures exist as such in the living microorganisms or occur in their disintegration products in tissues. In the biologic tests, the quantities of purified chemical fractions which were necessary to bring about the characteristic cellular changes were enormously greater than the quantity of living or dead tubercle bacilli which would be necessary to bring about equal changes.⁹

The lipid fraction studied by Anderson consisted of a mixture of many compounds including phosphatides, fats, waxes, and carbohydrates. The phosphatides, when injected into animal tissues, stimulate the proliferation of monocytes and promote their transformation into epithelioid cells. All of the lipid fractions have the property of stimulating similar reactions, due to the presence of phthioic acid, an optically active, liquid, saturated fatty acid, peculiar to the tubercle bacillus. They further cause the formation of multinucleated giant cells, either by facilitating the fusion of the cytoplasm of the monocytes or by stimulating their nuclei to divide amitotically while preventing subdivision of the cytoplasm. The bacterial waxes make up the bulk of the ether soluble substance. Chemically these are esters of higher hydroxy fatty acids with carbohydrates and with higher alcohols.¹⁵ They have a high molecular weight and are thought to be exclusively responsible for the acid-fast property of the bacilli. The protein fractions of the bacterial masses have been studied by Long and Seibert, Heidelberger and Menzel, and many others. The fully antigenic molecule of purified tuberculoprotein has been shown to have a molecular weight of 32,000, while that of old tuberculin (O.T.) is 16,000, and of purified protein derivative (P.P.D.) 9,000.¹⁶

FACTORS WHICH DETERMINE THE COURSE OF INFECTION

Dosage and virulence pertain to the invading parasite, while other known factors are related to the ability of the tissues of the host to combat the continuous multiplication of bacilli and prevent their dissemination.

Dosage.—Evidence from animal experiments has established beyond doubt that the size of the dose will determine whether an infection will be abortive, heal after an initial stage of expansion, or progress to the final destruction of the victim, provided that the virulence of the bacilli is within the limits commonly encountered in spontaneous infections.

Virulence.—The relative importance of virulence also must be appraised by analogy with animal experiments, for there appear to be practically no quantitative data on the factor of virulence of tubercle bacilli isolated from human infections, with the exception of rather scanty statistics on mortality rate in childhood infections with human and bovine strains.

Native Resistance.—Differences in native resistance to infection are both racial and individual. Available data in human families, comparable with those relating to the inheritability of susceptibility to cancer, are so scanty, however, that in arriving at this conclusion we rely more upon principles established by experimental work than upon direct evidence. The observation that in some human families there is a disproportionately large number of serious tuberculous infections does not prove a greater susceptibility in such families since magnified opportunities for infection may determine the high incidence. The evidence for differences in racial susceptibility is much more striking though perhaps no more real. In the United States great contrasts in racial susceptibility are observed in comparisons between the white population and the nonwhite minorities. In the most recent figures available, the death rate in nonwhites was more than three-fold that in the white population³ and, in the American Indian reservations, as much as tenfold.¹⁷ Even in comparisons between groups in which the economic status is comparable and in which the rate of infection, as determined by tuber-

culin tests, is approximately the same, the mortality rate is much higher in the Negro population. Morphologic studies of fatal cases indicate that the tissues of adult Negroes are generally less able to cope with tuberculous infections than are the tissues of adult whites. Caseous necrosis is much more extensive and fatal hematogenous generalization is more common.¹⁸

Age and Sex.—Native resistance to infections of many kinds, including tuberculosis, is not yet fully developed during infancy. This period shows the lowest incidence of tuberculosis but, relative to the number infected, the highest death rate. Resistance increases rapidly during the first five years of life and, in spite of a rapidly increasing rate of infection, the death rate is reduced during the period between infancy and puberty to a level more favorable than at any other phase of life. After puberty the rise is fairly rapid for both sexes but slightly more rapid for females until about the end of the child-bearing period when it drops off significantly, only to rise again sharply after 65 years. In males the upward curve continues from puberty onward but tapers off slightly after 75. It is constantly at a higher level than that for females after 25 and the total rate for males is about twice as high as that for females.³ The reasons for these tendencies are largely unknown.

The theory that observed differences in course and form in children and in adults may be explained as differences between the previously uninfected and those infected and immunized, is dependent upon the proof that the great majority of individuals have in fact been infected before reaching adulthood. It is probable that this was the case, at least among the inhabitants of the larger cities, in the early part of this century. More recent data from tuberculin surveys and results of anatomical studies show that the incidence of infection is much less at the present time. In an analysis of the figures from surveys made since 1930, Rich⁹ has pointed out the wide differences between the results obtained from various areas and in different economic classes. For instance, in the age group of 15 to 20 years, the figures vary from 23.3 per cent positive in Wisconsin high schools and University to 83.0 per cent positive in Philadelphia schools. Within the same age group, an average figure from the surveys in rural and urban groups, tabulated by Rich, was 42.7 per cent. Making a generous allowance for individuals who may have been infected at some earlier age but whose cutaneous hypersensitivity had disappeared, we can still safely assume that there is a fairly large residue of uninfected individuals in the teen age, probably near 50 per cent, but progressively diminishing in number in the older age groups.

The incidence of tuberculous lesions in autopsy material studied by Terplan¹⁹ during the decade between 1930 and 1940 was about 5.9 per cent in children below the sixth year and 19.4 per cent between 7 and 8 years in about

700 consecutive necropsies on children and young adults. In a smaller number of adult cases the percentage of positives in the age groups of 18 to 30 years was 71 per cent; 30 to 40, 78.4 per cent; 40 to 50, 90.4 per cent; and 50 to 90, about 97 per cent.

There are certain differences in form and location of lesions which are usually observed in infancy and early childhood on one hand and in adulthood on the other. These are: greater tendency in infancy and early childhood for the development of rapidly extending caseous lesions in the parenchyma, often with liquefaction and acute cavity formation; more extensive involvement of regional lymph nodes; more frequent hematogenous generalization and much greater frequency of tuberculous meningitis (70 per cent of fatal cases in Terplan's series); and the tendency for pulmonary lesions to occur in almost any part of the lungs in contrast with those of adults which show a pronounced predilection for the upper portions of the lungs. In part, the differences may be accounted for on the basis of an increased resistance to infection, acquired during the earlier part of life. If the greater resistance were attributable exclusively to acquired specific immunity following previous infection, we should expect often to see in the relatively large, previously uninfected portion of the adult population, particularly in young adults, progressive caseous complexes of the childhood type, frequently occurring hematogenous generalization, and tuberculous meningitis. Such is not the case. The form and course of progressive pulmonary tuberculosis in the white adult are much the same regardless of previous infection, so far as it can be determined from available evidence. The observed differences within the various groups can be accounted for more satisfactorily on the basis of differences of dosage and individual (inherited) differences in degree of susceptibility.

There is important anatomic evidence that the observed differences in susceptibility to infection are to some extent dependent upon age alone, that is, that they are dependent in some way upon the maturation of the tissues. As an undisputed example we have the fact that older children exhibit a superior capacity to resist infection as compared with those under 5 years of age. In this comparison, specific immunity cannot come into question because the great majority of children in these age groups have not come into contact with tuberculosis, as shown by tuberculin tests and postmortem statistics. Each successive age group shows a progressively less rapid course and, therefore, greater opportunity for fibrosis to occur, less extensive tuberculous lymphadenitis, and less frequent generalization. After threescore and ten, resistance seems to break down, not only with respect to tuberculosis but to many other bacterial infections as well. As pointed out by Long²⁰ and others, the greatly lessened incidence of tuberculosis among the population at large will in the future permit us to draw more certain conclusions concerning the influence of age upon the course and morphology of first infections.

Economic Status.—From the standpoint of preventive medicine the most important factor in the incidence of tuberculosis is poverty. This becomes evident in large masses of city dwellers where the conditions favorable for infection are provided by crowded housing, lack of facilities for, and knowledge of, elementary hygiene and by malnutrition. Statistically, the incidence of clinical tuberculosis is inversely proportional to the amount of the family income. It is generally conceded that the improvement in rates of incidence and mortality has been due to improvement of economic status and working conditions to a far greater degree than to any specific preventive measures that have been undertaken.

Occupation.—Persons in occupations which bring them into contact with large numbers of people in the lower economic groups where the greater number of active infections are found will necessarily be subjected to greater hazards of casual infection than others. Among these are physicians, nurses, and social workers. The rapid rate of increase in positive tuberculin reactors among medical students, interns, and student nurses is well known. There is not, however, a correspondingly great increase in incidence of clinically important infections among these groups, indicating that factors other than frequency of exposure to infection are the more important. Massiveness of exposure does not seem to be related closely to occupation. Of probable importance are the factors of excessive fatigue, lack of adequate rest regularly enjoyed, and all of the habits associated with occupation which tend to result in malnutrition. Many of these are undefined and intangible. Not so in the case of occupations in which certain kinds of dust are a hazard. Silica in finely divided form, when taken into the lungs as dust over a sufficiently long period of time and in sufficient quantities, not only leads to fibrous replacement of pulmonary parenchyma but exerts a specific effect in accelerating the progress of tuberculous infections which already exist or which may be acquired subsequently. This relationship between silicosis and tuberculosis of the lungs is discussed on page 663. The bland dusts such as carbon and iron oxide play no part as agents contributing to tuberculosis.

Concomitant Bacterial and Viral Infections.—The childhood diseases which appear to be followed in an extraordinary degree by active pulmonary tuberculosis are pertussis and measles with their accompanying bronchopneumonia. Influenza in the great epidemic during World War I seems to have brought to light a greatly increased number of cases of active tuberculosis, but the causal relationship has not been proved and the mechanism by which these diseases predispose to tuberculosis, if they do, is not known. A depression of the immune state by the coincident infection has been postulated without support of objective evidence. Clinical evidence appears to point to a scattering of exudates through coughing, in the presence of an already existing, active tuberculosis.

Malnutrition.—Deficiency of nutrition from any cause has long been recognized as an important contributing factor in the progression

of an already established infection, but tuberculosis is one of the important causes of malnutrition and, in individual cases, it may be impossible to determine which preceded the other. There seems to be no reason to question the opinion that the increased prevalence of tuberculosis which has occurred consistently in populations deprived of adequate food over periods of years, as in central Europe during World War I, has been due largely to malnutrition. Lack of protein seems to be most important. None of the supplementary factors has been shown to be of special importance. Ascorbic acid is destroyed more rapidly in infected than in normal individuals but when given in excess does not have any important protective or curative effect in tuberculosis.

Diabetes Mellitus.—Statistically the tuberculosis death rate is greater in untreated or inadequately treated diabetics than in nondiabetics, but when the diabetes is controlled with insulin, the difference is eliminated. Available evidence tends to exclude hyperglycemia, in itself, as an important factor. The mechanism by which resistance is depressed in diabetes, as in the case of malnutrition due to lack of sufficient food, is one of the important problems for further investigation.

ROUTES OF INFECTION

Pulmonary.—All primary pulmonary tuberculosis arises from the implantation into the lung of virulent tubercle bacilli which reach the parenchyma through the air passages. Infective sputum may be transferred directly, as by kissing or, more frequently, by droplets expelled into the air by coughing, sneezing, or talking and received in the mucous membranes of nose, mouth, or conjunctiva of persons nearby. The aspiration from the nose, mouth, or pharynx of the secretions thus contaminated may take place during any deep inspiratory effort, as an accident of deglutition, or during sleep when ciliary action is less effective and the cough reflex is depressed.

The theory that contaminated dust or infinitesimally small droplets may be inspired, reach the parenchyma through the air stream, and cause lesions in the human lung is hallowed by long acceptance but has many contradictions. One of the most obvious is that primary foci in the lung are typically single, while dust-borne infections or those due to direct implantation into the parenchyma of fine droplets would have the distribution characteristic of carbon pigmentation or silicosis and would certainly be expected to be multiple in the majority of cases.

Under exceptional circumstances, milk can be a source of pulmonary tuberculosis as proved by the postmortem findings in the Lübeck disaster (see page 243) in which many of the 77 fatal cases in infants showed advanced pulmonary lesions of the progressive primary type. These were shown to be due to accidents of swallowing and were not secondary to the tuberculous lesions in the intestines and abdominal lymph nodes. Generalization of infection from abdominal lesions will lead to disseminated bilateral miliary tuberculosis of the lungs but

not to single focal lesions resembling those of primary bronchogenic infections.

Primary Intestinal Infections.—First infections as a result of drinking milk from tuberculous cows have become a rarity in those areas of the world where compulsory elimination of tuberculous cows from dairy herds and pasteurization of milk have been put into practice. The mucosal ulcers which, in this type of infection, constitute the primary focus, tend to heal with little scar formation, giving rise to the belief that tubercle bacilli can pass through the intestinal mucosa to lymph channels and nodes without producing lesions in the intestine. In practically every case, the lymph node component of the "complex" soon becomes much more conspicuous and more important than the primary focus in the mucosa. Usually, several mesenteric nodes in the involved region enlarge and become caseous, later to calcify and become solidly encapsulated if the infection is overcome. In the very young, unsuccessful arrest of the lesions not infrequently permits dissemination through lymph and blood with the development of fatal miliary tuberculosis.

Tonsillar Infection.—The tonsils also may be the site of primary infection and, as in the intestine, the lesions tend to remain small, inconspicuous, and therefore easily overlooked. Rarely is there seen in the tonsil a large, caseous, or extensively ulcerated tuberculous lesion. The regional nodes are those of the cervical chain. The clinical picture of firm painless swelling of lymph nodes of the neck, known as scrofula, used to be a common sight but is now rare except in some parts of continental Europe and the British Isles, especially Scotland, where bovine tuberculosis is prevalent and pasteurization of milk is not generally practiced.⁶ In especially susceptible individuals, usually children, the cervical nodes enlarge up to the size of hen's eggs, fuse, become necrotic, and occasionally rupture to the surface, producing chronic sinuses in the side of the neck.

Skin.—Local infections of skin and subcutaneous tissue, with subsequent enlargement of the lymph nodes which drain the region, occasionally occur on the hands of butchers and other meat handlers and are sometimes spoken of as "inoculation tuberculosis." Physicians are sometimes infected through a break in the skin by contact with infectious sputum or by handling tuberculous tissues without gloves. Such lesions are self-limited and rarely lead to progressive infection of the internal organs.

REACTIONS OF THE TISSUES TO INJURY BY TUBERCLE BACILLI

Histologic Characteristics.—Since the immediate response of tissues to the presence of living or dead tubercle bacilli is a response to nonspecific injury, the early phase of the reaction consists mainly of hyperemia, edema, and leucocytic infiltration. This is true of both allergic and nonallergic tissues, but, for an equal infecting dose, the quantity of exudate is

greater in the former. The intensity of the inflammatory response is proportional to the size of the dose, larger masses of bacilli causing the greater degree of damage to the tissue and therefore stimulating greater degrees of hyperemia, edema, leukocytic infiltration, fibrinous deposit, and even hemorrhage. With minimal doses, the exudative phase may be so slight that it passes unnoticed and the invading bacilli may be destroyed by macrophages before they can become sufficiently numerous to cause specific lesions. The focus of infection which we

damaged or killed by them or their products. Damaged leukocytes and free bacilli are ingested by the large mononuclear cells which, with their accumulation of disintegration products of leukocytes and bacilli, enlarge, become crowded together, and assume angular shapes. Their cytoplasm becomes pale and sometimes foamy from high lipid content, resembling to a limited extent closely packed epithelial cells, hence the commonly used term "epithelioid cells." The compact mass of epithelioid cells constitutes the fundamental unit lesion of tuberculosis.

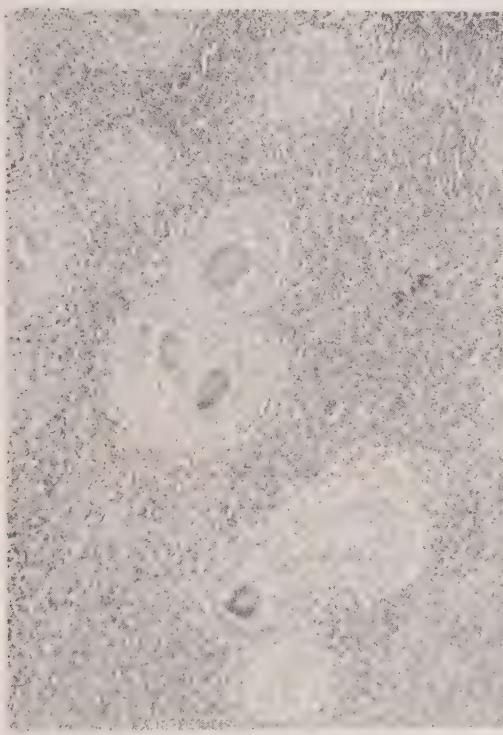


Fig. 156.

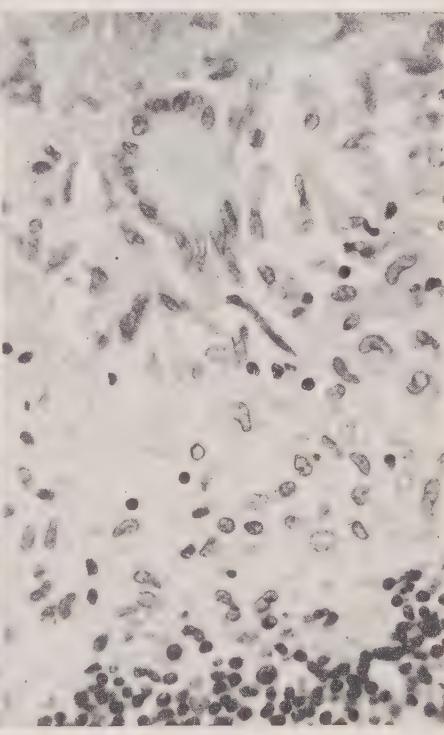


Fig. 157.

Figs. 156 and 157.—Epithelioid cell tubercles in lymph node. Fig. 156. Coalescent tubercles containing Langhans giant cells in center. Fig. 157. Details of structure of primitive tubercle with giant cell, epithelioid histiocytes, and zone of lymphocytes in periphery.

recognize as the tubercle is one which has passed into the second, more prolonged, phase, characterized by agglomeration of large mononuclear phagocytes. These are derived from blood monocytes and from mobilized tissue cells such as the septal cells of the lung and the reticular and littoral cells of the lymph nodes. During the initial phase, polymorphonuclear leukocytes ingest bacilli and are

In human tissues and in those of some laboratory animals, the presence of phospholipids and possibly of the waxes of the bacillary bodies causes fusion of the cytoplasm of the large mononuclear cells, with formation of multinuclear giant cells of the Langhans type in some portion of the primitive tubercle (Figs. 156 and 157). In the earlier stage, the multinuclear cell with peripherally arranged nuclei may

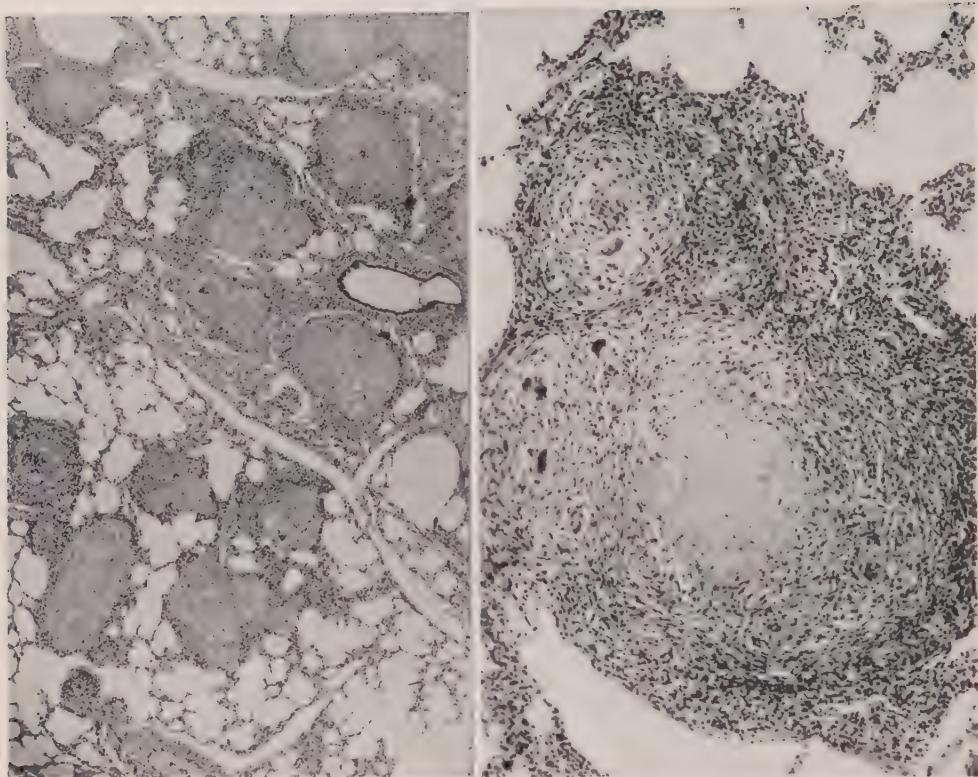


Fig. 158.—Miliary tubercles of lung. Right figure shows a single tubercle with caseous center and peripheral zone of lymphocytes and fibroblasts. A few multinuclear giant cells are irregularly distributed in the peripheral zone.

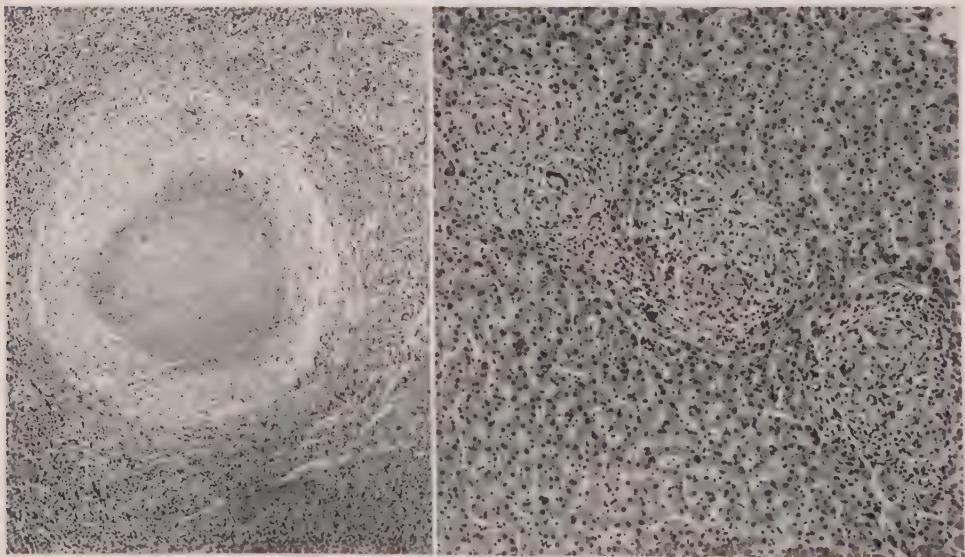


Fig. 159.—Left: Encapsulated caseous tubercle in spleen. Right: Epithelioid cell tubercles in liver.

lie in the center of the epithelioid cell tubercle, later to be destroyed by caseous necrosis. As the tubercle enlarges by the addition of more phagocytes at the periphery, giant cells are found in eccentric or peripheral position (Figs. 158 and 159).

In the slowly enlarging or healing tubercle, a poorly defined zone of lymphocytes is added to the outer part of the focus. It is the tubercle with its epithelioid cells, Langhans giant cells, and central mass of caseous necrosis upon which we rely usually for histologic diagnosis. It is the most characteristic lesion of the disease, though by no means found exclusively in tuberculosis. In rapidly expanding lesions, necrosis and exudation outstrip the proliferative component, providing insufficient time for the formation of tubercles and giant cells. Such is frequently the case in caseous pneumonia. The nature of the process is then recognized by the characteristic caseous necrosis and the presence of acid-fast bacilli in the lesions. When the process is slow and the reaction predominantly proliferative, it is usually difficult and often impossible to find the causative organisms in the macrophages or in the caseous masses of human tissues.

Macroscopically observable lesions are formed not so much by the progressive enlargement of single unit lesions ("histological tubercles") as by the coalescence of several of the smaller foci to form masses within the range of unaided vision. Discrete gray nodules of diameters ranging between approximately 0.5 and 2.0 mm. are called miliary tubercles because of their resemblance to millet seed. Caseation is frequently present in tubercles of this size (Figs. 158 and 159) but may be minimal or absent. The extent of necrosis is dependent much more upon the number of bacilli present than upon the size or even the age of the tubercle.

The terms "hard tubercle," to describe the compact epithelioid cell mass, and "soft tubercle," to designate the loosely formed mass of seminecrotic cells, have been introduced with the idea that these forms represent, respectively, successful and unsuccessful response to infection. This concept is unfortunate because it fails to take into consideration the fact that "hard" and "soft" tubercles may be present simultaneously in the same organ and, in this case, represent different stages of development

of the foci. In miliary tuberculosis of the liver, for example, the first stage is represented by foci of necrosis, the second by "soft" tubercles containing cellular detritus, polymorphonuclear leukocytes, and a few monocytes, and the third stage by compact masses of epithelioid cells, giant cells, and lymphocytes, i.e., "hard" tubercles (Fig. 159). This is not to deny the well-established fact, emphasized by Rich,⁹ that within the same tissue greater numbers of bacilli will invariably produce more necrosis than will small numbers.

Caseation.—Caseous necrosis differs from ordinary coagulative necrosis in two respects: It is characterized by high content of lipids, only a part of which is derived from the tubercle bacilli, and by the persistence of the necrotic substance for long periods of time, due probably to the presence of some constituent which inhibits the action of proteolytic enzymes. It is probable that the phosphatide of tubercle bacilli inhibits proteinase activity.²¹ Opie and Barker²² ascertained many years ago that monocytes have their greatest proteolytic activity when caseation is just beginning, and, when completed, all proteolytic activity has disappeared.

Since the term "caseation" is commonly used in designating any coagulative necrosis which occurs in tuberculosis rather than in a strictly descriptive sense, there is no agreement regarding its mechanism or time of development. Small foci of necrosis may appear in experimental lesions as early as two or three days after the time of injection. Complete caseation, as evidenced by the complete loss of cell outlines, by the presence of abundant lipids in the necrotic tissue, and by the tendency of the substance to stain strongly with eosin and appear homogeneous, begins to appear in experimental lesions in about two weeks after the injection of large doses of virulent bacilli in relatively resistant animals.^{23, 24} We have no reason to think that the required time is much greater or less in human tissues. There is no constant relationship between the degree or time of development of hypersensitivity and the process of caseation. If the dose is kept constant, the time of appearance of caseation may be later in previously immunized animals than in primary infections in spite of the hypersensitive state in the former, because cells of the immune tissue are better able to suppress the multiplication of in-

fecting bacilli. The tendency for caseation to occur in greater degree in young children than in older individuals is better accounted for on the basis of greater susceptibility to infection than by greater degree of hypersensitivity.

When in infected experimental animals the development of hypersensitivity is prevented by injecting into them at short intervals an excess of antigen, caseation is less than in animals which manifest hypersensitivity.²⁵ This evidence supports the view that hypersensitivity must be present before caseation can occur. Caseation is progressive so long as tubercle bacilli proliferate actively in the tissues and extension of the process continues to take place. When the activity of the macrophages is sufficient to destroy bacilli as rapidly as they are reproduced, effective encapsulation can take place. Fibrous capsules can provide protection against progressive caseation, however, only if complete. If continued bacterial growth is made possible by a supply of oxygen entering the lesion through a bronchus or bronchiectatic cavity, soluble decomposition products of tubercle bacilli (tuberculoprotein) may diffuse outward through the fibrous tissue of the capsule in concentration sufficient to bring about its complete necrosis.

Calcification.—The deposition of calcium salts in caseous lesions depends upon the diffusion of blood plasma into the tissue where its calcium can be precipitated in the form of relatively insoluble compounds. These are deposited at first in the form of scanty "clouds," irregularly distributed in the necrotic mass, and gradually increasing in density, especially at the periphery (Fig. 164). Gomori²⁶ has obtained evidence by histochemical methods that the form and site of preliminary calcification are determined by phosphatase activity in areas of recent necrosis. The progressive increase in density of the deposits, which is commonly observed in tuberculous lesions, must be explained on some other basis since evidence of phosphatase activity disappears after a short time. The presence of lipids in high concentration seems to have some influence upon the density and permanence of calcific deposits. The earliest evidence of calcification in ex-

perimentally induced lesions is seen at about the sixth week, and, in well-documented human cases (Lübeck infants), calcification has been observed in fifty-eight days but usually requires about a year to become sufficiently dense so that it can be recognized by x-ray examination of the living patient.

So far as is known, calcification is not in any sense a protective mechanism. A caseous focus may be infiltrated with lime salts in its center while teeming with bacilli at its periphery and there is rarely any envelopment of caseous substance by a calcific shell before the capsule is well formed. Sometimes interrupted scales form part of the lining of a cavity even at the time that bacilli-laden contents are being discharged through the communicating bronchus. In the final analysis, there is no protection of the organism from extension of a tuberculous infection except that provided by mobilized macrophages, which alone of all of the cells of the body have the power to destroy tubercle bacilli, and the mechanical barrier in the form of a fibrous capsule formed around masses of necrotic tissue. The presence of calcification in tuberculous foci in the lung indicates that necrosis has taken place in the past, but nothing more. It is not an evidence of healing.

INFLUENCE OF PREVIOUS INFECTION

Immunity.—The degree of effectiveness of acquired specific immunity in human tuberculosis is a question upon which the available evidence is insufficient to give a final answer. Opinions vary from one extreme to the other, some holding the view that it is of little or no practical consequence and its advantages are more than offset by the injurious effects of the hypersensitivity which accompanies it, while others have enough confidence in the protective value of acquired immunity to recommend some form of artificial immunization for the entire population. Experimental evidence supports a middle view, namely, that the immunity conferred by a benign infection is moderately advantageous in that it tends to protect against subsequent infections by doses of virulent tubercle bacilli which otherwise would be less successfully resisted. The hypersensitivity which develops to some degree with every immunizing procedure does not offset the protective value of the immunity. However, at best, the protection conferred is not of a high order. This view is supported generally by clinical and pathologic observations.

A degree of immunity can be induced experimentally by infecting animals with tubercle bacilli whose virulence has become permanently attenuated. After the extensive experimental work of Calmette and his collaborators²⁷ had demonstrated that such infections were harmless, human application of this method of immunization was instituted by Weill-Hallé in Paris,²⁸ and followed by similar clinical usage in many parts of Europe. The apparent effectiveness of the procedure was questioned because of the lack of adequate controls. More recent programs of experimental vaccination, such as those which have been carried out by Park and his associates²⁹ in New York, by Rosenthal and others³⁰ in Illinois, and by Aronson and Palmer³¹ in the American Indian reservations have been more carefully controlled and their results appear to be sufficiently advantageous to justify the more extensive use of the method. Mass tuberculin testing and BCG immunization, initiated in 1947 by the Danish Red Cross in Europe, now has been instituted on a worldwide scale. The strain of tubercle bacilli (bacillus of Calmette and Guérin) used in most of these experiments is of bovine origin and was used by Calmette and Guérin first in animal experiments and later in the extensive program for immunizing European children. The only major accident so far reported was that in Lübeck, Germany, where the harmless strain furnished by Calmette's laboratory was accidentally mixed with a virulent human strain and administered by mouth to 271 infants. Seventy-seven of these died from intestinal and pulmonary tuberculosis. There is no convincing evidence that the BCG strain of bacilli can acquire virulence to an extent sufficient to constitute a serious danger when administered to human beings.

Hypersensitivity.—The other aspect of altered reactivity, manifested by animals previously infected with living bacilli or repeatedly inoculated with dead bacilli, is hypersensitivity. The evidence that enhancement of protective immunity and the development of hypersensitivity are roughly parallel in their incipiency led to the belief that hypersensitivity is inseparable from protective immunity in spite of the contradictory fact that the degree of hypersensitivity is in no way correlated with the degree of resistance to infection in man or in experimental animals. More recent experimental work has demonstrated that immunity can be developed without evidence of hypersensitivity.³² Rich and his associates³³ have shown further that hypersensitivity can be abolished without at the same time destroying specific acquired immunity in previously immunized, hypersensitive animals. Another fact which supports the view that immunity and hypersensitivity are not merely different manifestations of the same phenomenon is that hypersensitivity may be produced by fully antigenic tuberculoprotein without conferring the least protective immunity against infection.³⁴

The principal result of hypersensitivity is an acceleration and intensification of the inflammatory reaction which follows when tubercle bacilli are introduced into the tissue. This in itself has no effect in limiting the spread of living

bacilli but rather the reverse in that the increased flow of tissue fluid tends to scatter them through the tissues and to increase the numbers reaching the lymph nodes by accelerating the flow of lymph. When the reaction reaches such an intensity as to cause the death of cells, it is clearly detrimental to the host. When necrosis occurs, the macrophages are not spared. Thus the only cells in the body which are known to be effective in destroying tubercle bacilli are themselves destroyed.

The mechanical barriers to the spread of infection consist principally of the fibrous capsules formed around caseous masses of tissue. These barriers also can be readily destroyed by caseous necrosis if the tuberculoprotein from necrotic centers reaches sufficient concentration. Similarly the capsules of caseous lymph nodes, the pleura, the walls of bronchi and blood vessels are involved and destroyed whenever the two conditions for necrosis are present, namely, hypersensitivity of the tissue and a sufficiently high concentration of tuberculoprotein at the site.

It should be emphasized that the state of hypersensitivity is present not only in individuals who have been infected at some previous time but also in first infections after an interval which varies from a few days to a few weeks. In itself a previously existing hypersensitivity cannot be considered to be decisively detrimental since in a matter of weeks, the factor of hypersensitivity will come into play whether in the child or adult, previously infected or uninfected.

It is not possible to account for the differences between the forms encountered in "childhood tuberculosis" and in "adulthood tuberculosis" by stating that the former is an infection in a nonallergic individual and the latter in an allergic (hypersensitive) one. After a comparatively short period of incipency, the child (or adult) who is infected for the first time is no less definitely hypersensitive than the adult who has been infected in early childhood. On the contrary, there is convincing evidence that hypersensitivity develops more quickly and to a greater intensity in childhood than in later life.

INFLUENCE OF THERAPY

In recent years many agents have been tested for therapeutic efficacy against tuberculous infections and, although many show striking inhibitory effects in vitro and in laboratory animal experiments, few have proved their worth in clinical use. At the middle of this century, streptomycin stood out as the most valuable agent although several others were still in use and many new antibiotics were being tried on an experimental basis. The principal limiting factors of streptomycin are associated with its toxicity, particularly for the eighth nerve, leading to deafness, and to the fact that after a course of several weeks' administration the infecting bacilli acquire resistance to its inhibitory effects. This streptomycin resistance is delayed by the simultaneous administration in appropriate dosage of para-aminosalicylic

acid which itself is relatively nontoxic and possesses moderate antibacterial potency in tuberculosis.

The effects of chemotherapy experimentally are comparable with those obtained by the use of tubercle bacilli in smaller dosage or of lesser virulence³⁵ and are attributable to a slowing of the rate of proliferation of bacilli in tissue. Sterilization of lesions by this means does not occur and, when therapy is discontinued or when bacillary resistance to the drug develops, the lesions often progress as before. There is little or no penetration of the larger caseous lesions or of the walls of old cavities and consequently the principal effects are obtained in the earlier exudative lesions of the lungs, in tuberculous leptomeningitis and in disseminated miliary tuberculosis. Observations made by postmortem examination of cases previously treated with streptomycin have demonstrated no specific features which were attributable to the effects of therapy. Quantitatively the lesions exhibit a greater degree of fibrosis with hyalinization, less caseation, and less tendency to form satellite lesions when compared with cases in which no chemotherapy has been employed.^{36, 37} Streptomycin is thought to interfere with division and with the utilization of metabolites necessary for bacterial proliferation.

ROUTES OF EXTENSION

Continuous or intermittent spread of infection takes place by any means whereby viable tubercle bacilli can be transferred from one susceptible tissue to another, including transport through lymphatic and blood vessels, along the mucous surfaces of respiratory and intestinal tracts, and over the surfaces of serous cavities.

Bronchogenic.—In adults, the route of extension which requires the most detailed consideration is the intrabronchial route. The slow erosion of infected parenchyma with formation of gradually enlarging cavities depends upon the maintenance of open communication between cavities and bronchial lumina. If the transfer of bacilli-laden exudate through bronchial lumina to areas of uninfected parenchyma can be prevented, the process usually becomes arrested. Spontaneous occlusion of small bronchi and bronchioles by plugs of exudate, inspissated mucus, and cellular detritus takes place readily in the young child whose tubes are small, soft, and easily collapsible. This structural peculiarity probably accounts, in part at least, for the smaller proportion of progressive pulmonary infections and the rarity of chronic cavities in children as compared with adults. This difference in tendency to spontaneous sealing off of the bronchial exits of tuberculous lesions has been observed in experimental animals of different ages. Young puppies show a tendency to the arrest and encapsulation of pulmonary lesions while older dogs show a higher percentage of cavities with open bronchial communications.²⁴

Thus the adult possesses a handicap in his fight against the slow progression of pulmonary infections in the form of larger and more rigid bronchi, which enable the process to perpetuate itself, in spite of pathologic evidence of a

greater inherent resistance of the tissues of adults by comparison with that of young children (the slower progress of infections, greater fibrosis, less caseation of lymph nodes, less hematogenous dissemination). The mechanism probably is not simply a matter of transfer of infective material from open cavity to uninfected area. As discussed previously, the tubercle bacillus requires a relatively large quantity of oxygen for its active growth. When a cavity is freely ventilated through an open



Fig. 160.—Far-advanced fibrocaseous tuberculosis with cavitation in lung of young woman. The characteristic localization of the more advanced lesions in the subapical portion of the upper lobe and apical one-third of the lower lobe are evident in this surgically removed lung. All cavities communicated by wide openings with larger bronchi.

bronchus, bacterial growth is rapid. Often, colony-like masses of acid-fast bacteria are found in the necrotic tissue and exudate which form the lining of the active cavity (Fig. 162), and proportionately large quantities of bacilli are found in the sputum produced from such cavities. If oxygen should be excluded from



Fig. 161.—Upper: Caseous primary complex in an aged adult. Note lamination of the unusually large primary tubercle (Ghon tubercle). Lower: Chronic fibrocaseous tuberculosis with multiple cavities in the upper lobe and caseous bronchopneumonia in the lower lobe. (Specimens in F. R. Zeit Museum of Pathology, Northwestern University Medical School.)

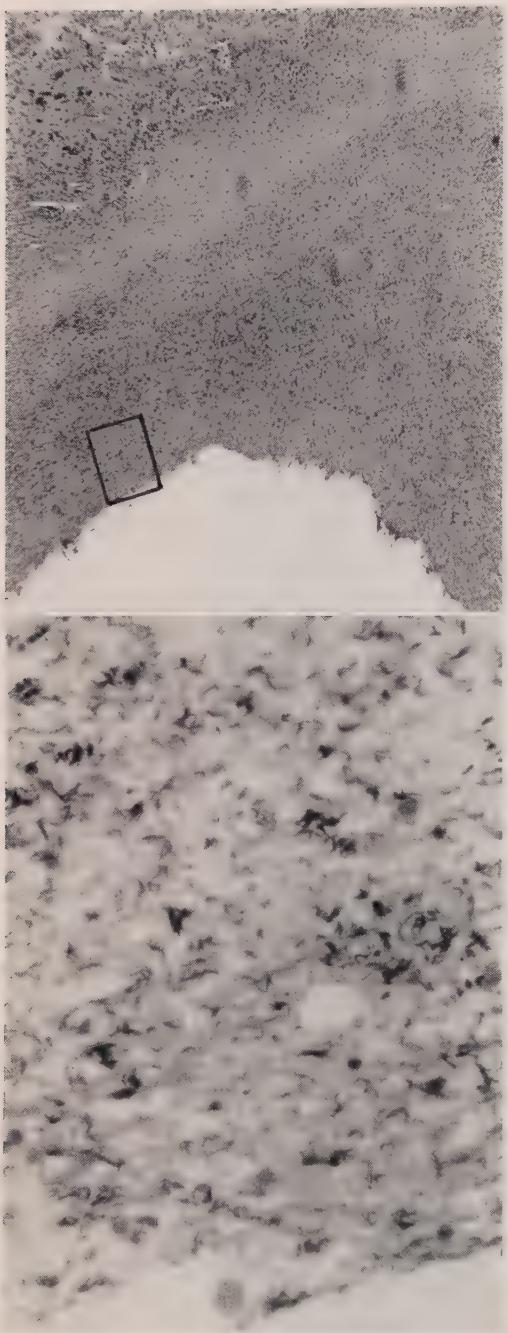


Fig. 162.—Upper: Low-power photomicrograph ($\times 60$) represents a section of the wall of a small cavity, stained by the Ziehl-Neelson method. The dark inner zone is formed by necrotic tissue and exudate, heavily laden with acid-fast bacilli; the intermediate zone consists of granulation tissue containing numerous epithelioid cells; and the pale outer zone consists of fibrous connective tissue. Lower: Higher magnification ($\times 660$) of the area represented by a small square in upper figure to show masses of tubercle bacilli in this zone.

such a cavity by the obstruction of its communicating bronchus, either spontaneously or therapeutically as by artificial pneumothorax, the bacilli cease to proliferate, their numbers are reduced by the action of phagocytes, and they cease to appear in the sputum. Occasionally in such a case the production of sputum ceases abruptly after institution of collapse therapy. In such an occurrence, one must assume the mechanical closure of the bronchus has been complete. In the more gradual conversion of a positive to a negative sputum, it is probable that slow "asphyxia" of the infecting bacteria has taken place.

Typically, in the earliest stages of clinically recognizable tuberculosis of the adult, the principal lesion is located in the dorsal or dorsolateral part of the upper one-half of an upper lobe, less commonly in the apex (Figs. 160 and 161). Progression takes place both toward the base and toward the apex. If a lesion breaks down rapidly, the softened masses of necrotic cells, mixed with bronchial mucus, may furnish a relatively large inoculum for superinfection of the patient's lung. Ordinarily, most of the exudate is coughed up and expectorated or swallowed. Some of it inevitably is drawn into adjacent bronchial rami to infect previously uninvolved parenchyma. The new foci are located most commonly in other portions of the same lobe in which the open cavity is situated. Next in frequency of involvement is the upper or middle portion of the upper lobe of the opposite side, but when the evacuation is massive, all portions of both lungs may be involved simultaneously. Such accidents give rise to widespread exudative and proliferative lesions which may lead rapidly to death from tuberculous pneumonia. The common course is more indolent. Instead of massive necrosis and rapid disintegration of the lesion, slow erosion takes place. The debris of necrotic tissue and clumps of macrophages become mixed with the thick mucus of the irritated bronchial mucosa and, for the greater part, are propelled by the cilia along mucosal surfaces. From the distribution and size of the more recently formed lesions it must be assumed that reaspiration of some of the exudate into the bronchioles of adjoining lobules takes place, but it is difficult to understand how thick, scanty mucopurulent exudate can be drawn into small bronchi and bronchioles in a direction opposite to that of ciliary action. It is conceivable that the principal spread occurs at times when secretions are thin, due to irritation of upper respiratory infections and of irritating dusts and gases. Under these conditions, the bronchial "drift" would be aided by gravity.

Lymphogenous.—From any heavily seeded focus or one in which bacilli are proliferating actively, there will be some escape of infected phagocytes into the lymph spaces. Dissemination takes place freely during the first few weeks of a first infection but less freely after active immunity is established. When the bacilli reaching the lymph nodes are sufficiently numerous to escape rapid and complete destruction, they initiate secondary foci of inflammation with tubercle formation. In the adult, these foci are characteristically small and in-

conspicuous, with little or no caseation (Fig. 157). It is inaccurate to say that the lymph nodes of the adult usually are not involved, even in the previously infected, immunized individual, for, if there is an active tuberculous lesion in the lung, there is always evidence of hyperplasia and macrophagic activity in the lymph nodes which drain the involved area. Usually, compact agglomerates of epithelioid cells can be found, but giant cells may be absent and stainable acid-fast bacilli are rare. In the bronchopulmonary lymph nodes of the infected infant or very young child, caseous lesions are usually extensive, often more extensive than the focus in the parenchyma. In the older child, the degree of involvement and extent of caseation occupy an intermediate position between that of the highly susceptible infant and the much more resistant adult.

Hematogenous.—From every active pulmonary lesion, whether in child or adult, previously infected or infected for the first time, there is some escape of tubercle bacilli into the blood stream. This is not entirely dependent upon their escape through the lymphatic channels and thence into the blood. Evidence from post-mortem examination of human tissues and from animal experiment indicates that hematogenous dissemination depends upon escape of bacilli directly into the pulmonary venules which lie within areas of infection at least as much as upon lymphatic extension. Less commonly, caseous nodes lying in contact with venous walls become eroded and shed bacillus-laden cells more or less continuously into the blood. In the latter case, blood-borne dissemination will be massive and generalized miliary tuberculosis will result. (See page 257.)

Mucous and Serous Membranes.—The upward sweep of cilia in the respiratory tract is so effective in keeping the tracheobronchial mucosa cleansed of bacteria that tubercles and ulcers in this location are rare except in far-advanced cases of ulcerative pulmonary tuberculosis. The absence of cilia on the vocal cords and portions of the aryteno-epiglottic folds permits stasis of sputum in the upper one-third of the larynx, and at this level specific lesions are much more common. The rapidity of downward passage of gastrointestinal contents and the factor of dilution with food and secretions aid in preventing the formation of tuberculous lesions in esophagus, stomach, and upper portion of intestine, and it is only in the lower part of the ileum and in the cecum that tuberculous ulcers are found with great frequency. The factors favoring infection at this level are sluggish movement of intestinal contents, absorption and concentration of contents, and the presence of many foci of lymphoid tissue in the form of solitary and aggregated follicles. Tubercles and ulcers appear to form more readily at the sites of lymphoid aggregates but it is unlikely that the presence of lymphoid tissue is of sufficient importance to deserve the emphasis usually given it. The lower part of the rectum also is involved with ulcerative lesions in an important number of cases of advanced pulmonary tuberculosis, while the colon between the cecum and rectum is usually spared, again pointing to stasis as one of the

determining factors in the localization of intestinal lesions. (See also page 780.)

Serous membranes are the site of extensive exudative lesions only when inoculated with large numbers of tubercle bacilli from the disintegration of contiguous necrotic lesions. In the case of the pleura, necrotic foci in the lung break through the pleura and infect it (Fig. 169). Tuberculous pericarditis, a comparatively rare event, occurs by direct extension from pleura or mediastinal lymph nodes. The peritoneum is most commonly involved by extension of an intestinal ulcer to its surface or rupture of a caseous mesenteric node. The formation of serofibrinous exudates tends rapidly to disseminate the infective agent throughout serous cavities. Hematogenous miliary tuberculosis of pleura, peritoneum, or pericardium is rarely the cause of exudative lesions of these membranes since the tubercles are small, localized, and predominantly proliferative. (See also page 801.)

RELATIVE SUSCEPTIBILITY OF VARIOUS TISSUES

The relative frequency with which tuberculous lesions are formed in different tissues is not the same in susceptible individuals as in the more resistant, and, therefore, is not the same in the infant as in the much more resistant adult. In the infant, important lesions are found in lymph nodes in practically 100 per cent of infections; the meninges become involved with great frequency and lesions often become established in the spleen, differing sharply from the typical findings in adults. Similar differences are found in experimental animals of widely different susceptibility, the more resistant animals such as rabbits and dogs ordinarily showing the greater number of progressive lesions in lungs and kidneys, while in the susceptible guinea pig the pulmonary lesions are relatively inconspicuous and more extensive lesions are found in liver, spleen, and lymph nodes.

Too little is known of the factors involved to permit a satisfactory explanation of these differences. The number of bacilli arrested by the tissue will obviously have considerable bearing on the question. Experimentally, particulate matter in general and tubercle bacilli in particular are filtered out of the circulating blood to a large extent by the lungs, liver, spleen, and bone marrow and in other organs and tissues in lesser degrees. In the lungs, the process is largely a matter of mechanical filtration since few of the pulmonary macrophages are in contact with the circulating blood. In other organs the number of bacilli arrested is roughly proportional to the number of macrophages which are in contact with the blood. If the arrested bacteria are sufficiently numerous, any degree of local resistance will be overcome. Differences in inherent susceptibility are exhibited when dosage is comparatively small, the more resistant tissues showing small, abortive, or arrested lesions and the less resistant tissues allowing lesions to progress.

In the human adult, the lung is considered to be the most susceptible tissue, due in large

part to its high content of available oxygen. When the oxygen is partially excluded as in therapeutic collapse or in spontaneous pneumothorax, the great differences in susceptibility between pulmonary and other tissues tend to disappear. This conclusion is supported by more exactly controlled experiments in laboratory animals.³³ At the other end of the scale of susceptibility are such tissues as the myocardium, skeletal muscle, stomach, pancreas, thyroid, and testis which are involved with great rarity. In an intermediate group are the adrenals, kidneys, fallopian tubes, epididymis, brain, meninges, and other serous membranes which are the site of progressive destructive lesions with greater or less frequency.

It is difficult to appraise the relative susceptibility of lymphoid tissue. Some of the lymph nodes are involved whenever there is a tuberculous focus anywhere in the body, so that their frequency of involvement may be considered to be 100 per cent. In the infant, infection of lymph nodes usually means progressive involvement, at least for a time, frequently with massive caseation, but in the adult, lymphoid tissue exhibits remarkable resistance to destructive infections. Even in the presence of progressive and fatal pulmonary tuberculosis with hematogenous dissemination of infection throughout the body, the lymph nodes may show very little disease.

Red bone marrow, along with liver and spleen, is not only involved regularly in generalized hematogenous tuberculosis but is often the seat of progressive tuberculosis in children. While involved with comparable frequency, the liver and spleen do not form a favorable site for proliferation of tubercle bacilli and lesions usually regress, resolving completely or leaving small caseous foci which sooner or later become calcified. Tracheobronchial, laryngeal, and intestinal mucosa in the adult must be considered as highly resistant membranes. Lesions in these locations are ordinarily few and of limited extent, and tend to heal rapidly when the source of infection is eliminated. The same features are observable even in primary infections of the intestine in children, where infected mesenteric lymph nodes often constitute the only evidence of abdominal infection.

MORPHOLOGY OF PULMONARY LESIONS

The Primary Complex.—When the tissues of a susceptible individual are infected for the first time with virulent tubercle bacilli in quantity sufficient to produce a recognizable lesion, the result is termed a "primary focus." This lesion usually occurs in the pulmonary parenchyma but may also develop in the tonsil, in the mucosa of the intestinal tract, especially of the lower part of the ileum and cecum or, more rarely, as a nodule in the skin. Regardless of location, some of the bacilli will reach the lymph nodes

which drain the area and initiate in them secondary lesions which frequently enlarge and caseate. Small nodules of tuberculous tissue may be formed along the lymph channels which lead to the involved nodes. The primary focus with the involved lymphatic channels and nodes is called the primary tuberculous complex (Figs. 161, 162 and 163). In the lungs of infants and young children, the parenchymal component may be located in any part of the lung, including the base and apex, but most commonly the primary focus is found in the middle portions of the lungs immediately beneath the pleura.

Nothing is known of the earliest stage of development of the primary infection in the human lung since the earliest recognizable primary foci which have been described were already caseous and therefore at least a few weeks old. We must depend upon analogies with the findings in experimentally infected animals for this information. Since the caseous primary complexes and all of the later stages of canine infections²³ much more closely resemble those of human infections than do those of guinea pigs and rabbits, it is probable that the early stages of human and canine lesions also will resemble each other.

In previously normal young puppies, the lesion begins as a poorly defined inflammatory focus in the form of a peribronchiolar exudative pneumonia.²⁴ Neutrophiles predominate at first and are gradually replaced by large mononuclear cells which, during a period of about a week, are transformed into epithelioid cells. By this time the lesion has become solid in the center and has expanded peripherally by extension through bronchioles and from alveolus to alveolus. Caseation begins to appear as early as the end of the second week. The fibrous capsule forms at the periphery of the caseous portion and the less dense inflammatory zone outside of the capsule resolves, leaving a residue of thickened alveolar walls and vesicular emphysema just outside of the capsule (Fig. 163). Slight calcification may appear as early as six weeks in young puppies and 58 days in infants, but ten months to a year or more may elapse before calcification is sufficiently advanced to be visible in roentgenograms. Calcification occurs much more readily in infants and young children than in adults.

While the parenchymal focus is passing through its cycle of enlargement, caseation, arrest, and encapsulation, the lymph node component of the complex is undergoing similar development. In the previously uninfected infant and young child, the lymph nodes usually become involved to a greater extent than does the lung at the site of primary focus.



Fig. 163.—Calcified primary complex. The encapsulated primary nodule is attached to the thickened pleura. Calcified caseous lymph nodes are located in the hilum. (Specimen in F. R. Zeit Museum of Pathology, Northwestern University Medical School.)

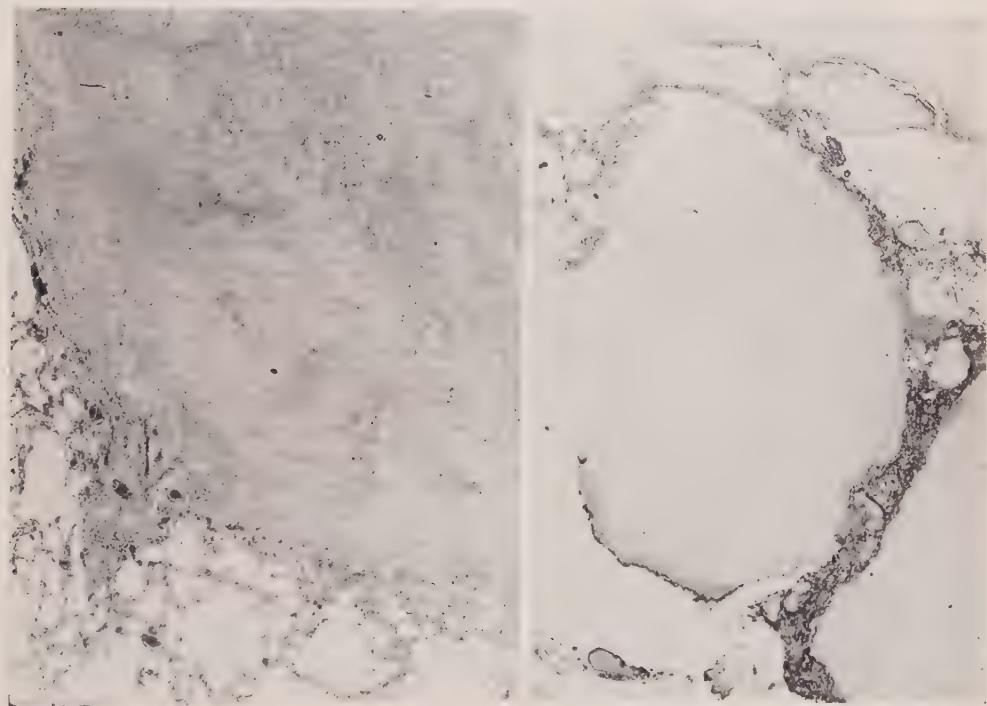


Fig. 164.—Left: Encapsulated primary focus in lung. Low magnification photomicrograph.
Right: Caseous lymph node with calcification at margins of caseous masses.

The hilar nodes which drain the site are first to be involved, then the tracheo-bronchial, and sometimes the paratracheal chain of nodes in succession. It is usual for the greatest enlargement and most extensive caseation to occur in the hilar nodes, regional to the site of infection, and consequently the calcified residues are usually found in one or more nodes of the hilum on the side affected (Figs. 161 and 162). The great majority of such lesions become arrested and encapsulated by dense fibrous tissue. The caseous masses if very small may disappear, leaving only a small scar of the pulmonary parenchyma and thickening of the overlying pleura. More commonly the caseous substance becomes chalky from absorption of calcium, then stony hard, and the residue when seen many years later consists of a calcified nodule from 1 mm. to 2 cm. or more in diameter, encapsulated by dense collagenous tissue and often blackened by carbon dust. In rare instances the calcified nodule in the parenchyma may be several centimeters in diameter. The larger lesions often show concentric lamination (Fig. 161). In the caseous substance of encapsulated nodules, tubercle bacilli may survive for many months, but gradually die out and, by the time calcification is well advanced, most of the masses are incapable of initiating tuberculosis in guinea pigs.³⁹ After a lapse of many years the calcified nodule in parenchyma or node may be transformed into bone. The process of ossification ordinarily requires ten years or longer, according to Sweany.⁴⁰

The phenomenon of extensive involvement of the regional lymph nodes in first infections is characteristic of the infant and young child but is also seen frequently in adult Negroes and occasionally in unusually susceptible individuals of any race. In the older child this tendency is diminished by comparison with the younger age group. In white adults, the caseous residues in lymph nodes are usually small, sometimes absent and rarely massive. Those who believe that the tendency of infections to spare the lymph nodes is due exclusively to acquired specific immunity attribute this phenomenon in adults to gradual immunization of all adults by the inhalation of small doses of tubercle bacilli, too

small to produce a visible lesion. Such a theory is difficult to disprove and impossible to prove for human tuberculosis, and data derived from animal experiments are conflicting.

Progressive Primary Infections.—Instead of undergoing successful arrest, encapsulation, and ultimate sterilization, the lesions resulting from first infections in exceptionally susceptible individuals and in some with average resistance, but subjected to overwhelming infection, will progress by various stages until widespread disease occurs. These progressive infections are found more often in infants (Fig. 165) and in children under 5 years and more often in Negroes at any age than in Caucasians at comparable ages, but occasional examples of progressive primary infections can be found in older white children and in white adults.

As in the case of arrested primary foci, the lesions of progressive primary infection may be located in practically any part of the lung. The principal focus frequently consists of a roughly pyramidal mass of caseous necrosis with its base on the pleura. Its form is determined by the form of the bronchial tree, through the lumina of which the infective exudate is distributed. Widespread bronchial dissemination takes place in the majority of cases by one of two methods. In the first, some portion of the caseous mass in the pulmonary focus becomes softened, gains access to the lumen of a small bronchus, and the bacilli-laden necrotic tissue and exudate are distributed through the bronchi to previously uninvolved tissue of both lungs. The other source of infective material in progressive primary lesions is caseous lymph nodes. The nodal source is more important in the youngest age group and less so as adulthood is approached. In such cases, progressive enlargement and necrosis of a hilar or intrapulmonary lymph node involve an adjacent bronchus. The bronchial wall becomes necrotic and caseous matter escapes from the softened lymph node into the bronchial lumen. The tuberculous bronchopneumonia which ensues is often progressive until death. Not all cases of progressive primary infections terminate fatally, however. Retardation of the infection and complete arrest may occur at any stage of the

process. Portions of the exudate resolve, caseous masses become encapsulated and calcified, leaving multiple, comparatively large calcified and fibrous residues.

Chronic Fibrocaseous Tuberculosis (Adult Type).—The principal characteristics of pulmonary tuberculosis in adults, and this will necessarily include some older children, are the quiet symptomless onset, indolent prolonged course, frequent location in the apical one-half of an upper lobe, tendency to slow erosion of consolidated parenchyma with cavity formation and comparatively slight involvement of lymph nodes. These are, in part,

in the upper lobes and the chronic cavitation which serves to perpetuate the infection.

To those who accept the view that the human adult is highly resistant to tuberculous infection and will therefore require large doses of infectious material to bring about a progressive lesion, a satisfactory explanation for localization in the subapical region is found in the "gravity theory." The areas most frequently affected are supplied by the dorsal rami of the superior bronchi of each side (bronchus dexter eparterialis and ramus bronchialis hyparterialis I). These, with their dorsally inclined apical rami and the axillary branches of the lower lobe bronchi, are the channels into which viscid liquids flow most



Fig. 165.—Progressive primary tuberculosis in 18-month-old infant. Posterior view of sectioned lungs. Coalescent bronchopneumonic lesions of right upper and middle lobes; acinar-nodose tuberculosis (peribronchiolar lesions) of left lung and right lower lobe; caseous tuberculosis of bronchopulmonary and tracheobronchial lymph nodes.

the characteristics of infections of the more resistant as compared with the more susceptible laboratory animals. To some students of the subject, acquired specific immunity accounts for all of the observed differences between infections in the young and in the old, but to others, age-determined factors also play an important part, enhancing the protective effects of acquired immunity when present. Greater resistance to infection does not explain satisfactorily the pronounced tendency for lesions to occur and remain localized

readily when the subject is in a reclining position, i.e., supine or partly turned to one side or the other.^{41, 42}

In discussing routes of extension, it was suggested that the small, more readily collapsible and therefore easily obstructed bronchi of children might, in part, account for the fact that chronic cavities are rare until adulthood. The larger, more rigid bronchi of the mature individual, when involved by extension from surrounding tuberculous parenchyma, remain open and prevent spontaneous healing by maintaining the oxygen supply to the infected tissue. Thus, in spite of the comparatively high resistance of adult pulmonary tissue, enlargement by direct extension and intrabronchial dissemination may continue indefinitely.

The question of relative importance of reactivation of primary lesions and of exogenous reinfections in the development of progressive fibrocavous tuberculosis in adults has not been settled. The reactivation of a lesion which has become temporarily arrested is not in the pathologic sense a "reinfection" but rather the delayed progression of an already established lesion. In an accurate use of the term, the only true reinfection which is possible is one acquired from exogenous sources in an individual who has overcome completely one or more previous infections. It seems wise, therefore, to adopt the definitions and terminology used by Terplan¹⁹ and speak of "post-primary progression" if the process is an extension of a temporarily quiescent primary lesion, of "reinfection" if a subject with a healed process again becomes infected from without, and of "superinfection" when one with an unhealed lesion acquires a new exogenous infection. The term "endogenous reinfection" should be abandoned as inaccurate and confusing.

The first objective evidence of early tuberculosis in the adult, as in the child, is obtained from systematic routine tests for cutaneous hypersensitivity to tuberculin and from x-ray examination of the chest. At about the time the tuberculin test becomes positive, which has been observed to vary in clinical cases from two to several weeks from the time of a known exposure, irregular areas of increased density may be observed in roentgenograms of the chest. The location as a rule is in an upper lobe at about the level of the clavicle or below it. A dorsal position of the lesion will cause it to appear just above the hilum in the antero-posterior view, but when located more laterally the mottled shadow may be roughly triangular or "fan-shaped," with the base of the triangle on the pleura and its apex directed toward the hilum. It is, at present, customary in clinical work to consider these as "reinfection" lesions, regardless of objective evidence of previous infection, on the grounds that its form and subapical position are, in some way, determined by previous infection. This view is justified to the extent that morphologic studies have demonstrated in the majority of such cases evidence of previous infection in the form of typical primary complexes. Some of these bronchopneumonic "infiltrates," however, apparently represent first infections⁴³ and there can be no certainty about any individual case except by a competently executed examination of postmortem material. These subapical lesions com-

monly reach a maximal extent and density within a few months and then gradually clear, leaving only fibrous scars but sometimes with small calcified residues in the parenchyma. The lymph node component of the complex is seldom apparent in x-ray films when the subject is an adult.

The character of the parenchymal lesion in its early stage is that of a localized, dry, confluent bronchopneumonia. Edema is minimal. Histologically the lesions are both exudative and proliferative but predominantly the latter. Monocytes, epithelioid cells, fibroblasts and multinucleated giant cells form the characteristic picture. Some degree of caseation is almost invariably present in the centers of the denser lesions. The resolution of such masses is never complete anatomic ally and scarring may be extensive even though the density is insufficient to be detected antemortem by x-ray examination. Evidence of previous infection remains indefinitely in the form of fibrous thickening of the pleura over the site of infection, ramifying pigmented scars in the parenchyma, sometimes containing one or more encapsulated caseous calcified nodules. Pronounced vesicular emphysema frequently occurs in the area of thickened alveolar walls and fibrosis, but this is not a specific alteration as it occurs in any diffusely fibrotic pulmonary lesion in which the air spaces are not entirely obliterated. Caseous residues in the hilar lymph nodes are exceptional in this type of lesion.

A variable and statistically undefined number of these infections continue over a period of months or years to increase in density and to expand in all directions. The dense central portions undergo caseous necrosis. Softening of the necrotic substance takes place slowly within the area and leads to disintegration of some portion of the bronchial walls. This is the beginning of cavity formation and introduces a double disadvantage to the tissues of the infected host. It accelerates the rate of proliferation of tubercle bacilli by supplying through the involved bronchi the necessary oxygen which, in a closed lesion, is insufficient to support growth, and it provides a means of dissemination of infective necrotic tissue and exudate. The necrotic lining of a cavity which freely communicates with the

lumen of an open bronchus is frequently loaded with acid-fast bacilli (Fig. 162), while, in the tissue a few millimeters from the surface, it may be difficult to find any.

At the periphery of an excavating lesion, beyond the zone of necrosis, a zone of fibrous tissue is formed which tends to prevent further peripheral extension of the inflammatory process. This fibrous wall is incapable of limiting peripheral extension so long as free communication between cavity and bronchial lumen persists. Bacilli continue to proliferate in the lining of the cavity, which slowly enlarges by continuous necrosis and erosion. New fibrous tissue continues to be formed on the outside of the capsule, encroaching upon a progressively greater mass of parenchyma and fusing with the satellite lesions at its periphery. Such a process often continues for many years, gradually converting an upper lobe or even an entire lung into an empty shell of dense fibrous tissue. Large cavities usually are trabeculated and often are multilocular, due to uneven peripheral progression or to coalescence of two or more smaller cavities formed simultaneously (Fig. 160). Coarse trabeculae and single or branching cords of fibrous tissue which so often traverse these old cavities contain obliterated blood vessels and bronchi which are more resistant to erosion than is the parenchyma of the lung. Hemorrhage rarely occurs from the vessels in these trabeculae because of previous obliteration by organized thrombi. Hemorrhage is ordinarily the result of erosion by a rapidly extending caseous process of small vessels in the outer wall of a cavity.

The principal direction of extension is toward the base of the lung from the site of the principal lesion, usually in upper or middle third of an upper lobe, so that in roentgenograms or at the autopsy table the oldest and most advanced lesions are found in the upper part of the lung and successively less advanced lesions are found in progression toward the base (Fig. 161). As a rule, the ventral portions of the lungs are spared. The oldest and most extensive lesions are, with rare exceptions, located dorsally or dorso-laterally. Wherever an exudative lesion lies near the pleura, the serous membrane becomes thickened, roughened, and, following organization of the fibrinous exu-

date, dense fibrous adhesions are formed between visceral and parietal surfaces (Fig. 166). After repeated effusions into the pleural spaces or following tuberculous empyema, the fusion of pleural surfaces becomes extensive in dorsal and diaphragmatic areas, sometimes completely obliterating the space in all portions.

Acinar Lesions.—In the ordinary case of upper lobe infection in adults the erosion of consolidated parenchyma and of involved bronchi is slow. Most of the cellular debris is incorporated into the bronchial mucus, swept upward into trachea and larynx, and expectorated or swallowed. Small quantities are reaspirated or "drift" into other bronchial rami, and new lesions are initiated in the respiratory bronchioles and alveoli. Although the tissues may have attained a high degree of hypersensitivity to tuberculin-protein, no rapidly necrotizing lesions are formed in the new foci because the numbers of bacilli are small. Exudation of leukocytes and fibrin occurs but is quickly overshadowed by immigration of mononuclear phagocytes with the formation of epithelioid cell agglomerates and giant cells. The gross form of the lesions is determined by their bronchiolar distribution. They appear as exudate-filled alveolar sacs in clusters around terminal bronchioles. Early, they are gray and slightly translucent. Later, with enlargement and caseation, they become yellow-white and opaque.

Tuberculous Pneumonia.—So long as the "spill" from gradually eroding cavities remains small, the new lesions which result from intrabronchial transmissions of infection tend to be limited to the lobe which contains the cavity, with slow extension toward the base and toward the apex. With the acceleration of the necrotizing process, larger quantities of liquefying or crumbling necrotic tissue and exudate are produced within the cavities and involved bronchi, providing opportunities for the wider dissemination of infective material. The conditions believed to be necessary for the production of extensive exudative tuberculosis of the lung are the introduction into hypersensitive tissue of large quantities of antigen (whole bacilli or their degradation products). While the conditions are

not strictly comparable with those of the experiments of Koch, in which he injected large masses of tubercle bacilli under the skin of previously infected hypersensitive guinea pigs, this process in the human lung is generally considered to be analogous to the Koch phenomenon. Large quantities of exudate, containing tubercle bacilli and impregnated with tuberculo-protein, reach uninjected tissue which is already hypersensitive, precipitating a

Typically, when viewed at postmortem examination, the lobes exhibiting the more extensive lesions contain confluent masses of exudative consolidation. Within these are larger or smaller masses of caseous substance, while in the lobes of the opposite lung the peribronchial lesions, though widely disseminated, are much less extensive. The more recently involved areas of exudative pneumonia are translucent, gray, and smooth, the exudate re-

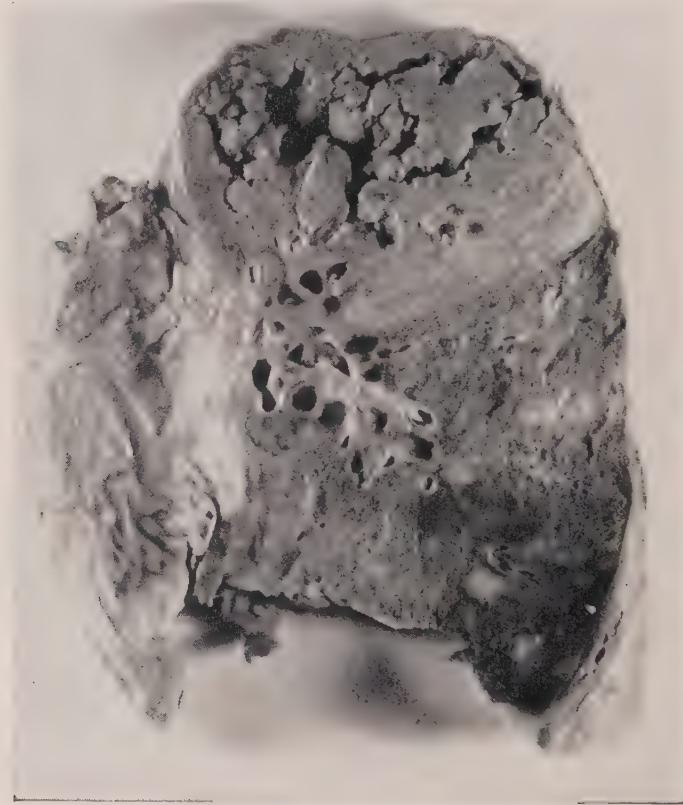


Fig. 166.—Caseous pneumonia in young woman. Complete caseation in upper lobe, thickened pleura, and caseous exudate over lower lobe. (Specimen in F. R. Zeit Museum of Pathology, Northwestern University Medical School.)

vigorous inflammatory response. Qualitatively the exudate is the same as that produced in the lesions of first infection, but the vigor of the response is greatly enhanced and the exudate much more abundant, consisting of edema fluid, fibrin, polymorphonuclear leukocytes, monocytes, lymphocytes, and, sometimes, considerable numbers of erythrocytes. Necrosis of tissue ensues rapidly. Adjacent foci enlarge and coalesce.

sembling inspissated edema fluid ("gelatinous pneumonia") Caseous necrosis occurs in the older masses and begins around the bronchi in the central parts of the lesions. In exceptional cases, an entire lobe undergoes caseation (Fig. 166) ("diffuse caseous pneumonia"), appearing in macroscopic section as firm, dry, opaque, yellow-white substance with only the usual gray or black markings of anthracosis remaining to identify the struc-

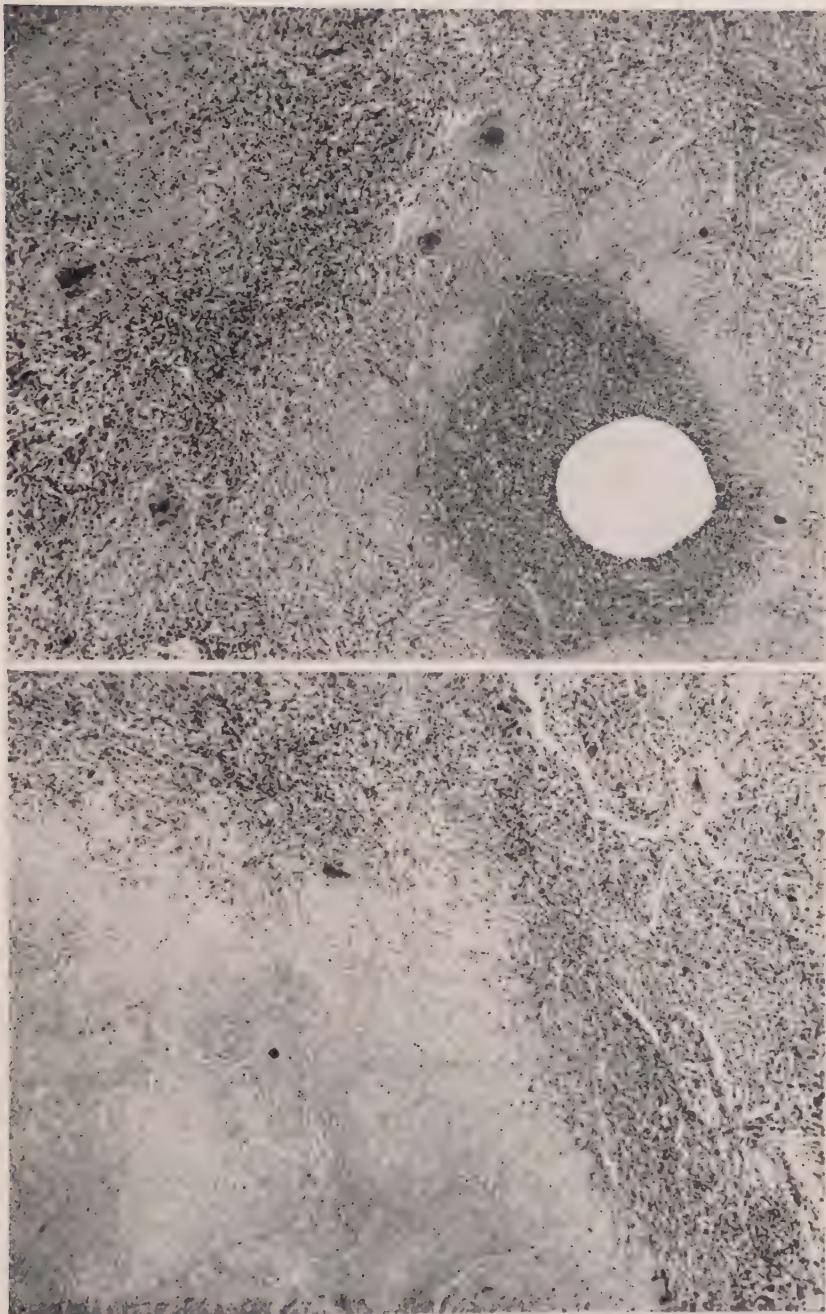


Fig. 167.—Upper: Caseous bronchiolitis and bronchopneumonia. Vacuole marks site of lumen of bronchiole. Lower: Caseous bronchopneumonia. Evidence of early organization of exudate above and to the right.

ture. Usually death occurs before caseation of an entire lobe is complete. Resolution of the exudate is possible up to the time that necrosis occurs. Fibrous organization occurs in caseous areas provided that the patient survives.

Microscopically, in the "gelatinous stage" the alveoli are found to contain precipitated protein, large numbers of monocytes and alveolar macrophages, and smaller numbers of neutrophiles, lymphocytes, and plasma cells. Alveolar walls

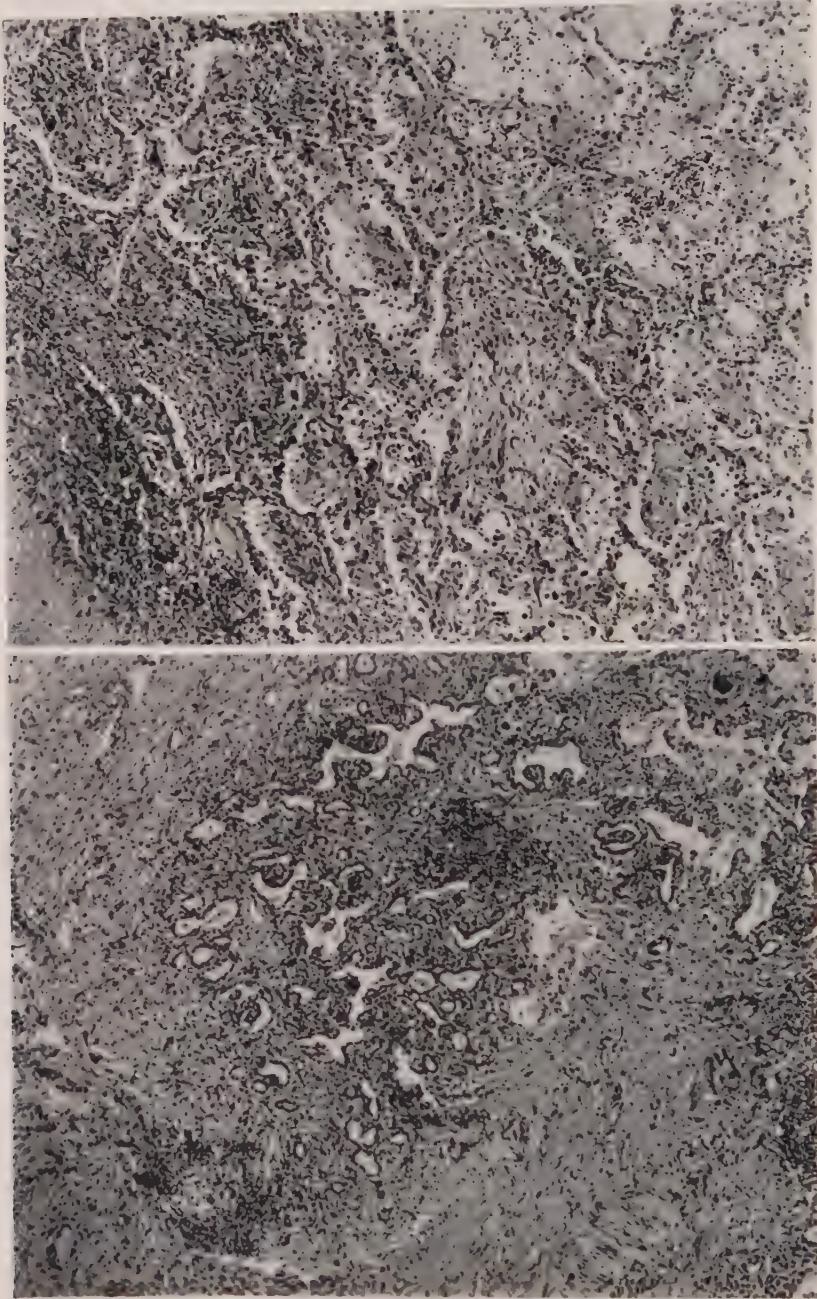


Fig. 168.—Upper: Organization of alveolar exudate in tuberculous pneumonia. Lower: Fibrosis of old tuberculous lesion. The remaining air spaces (probably respiratory bronchioles) are lined by cuboid epithelium and surrounded by infiltrates of lymphocytes.

are thickened but intact. These areas or zones merge with zones which contain more fibrin and leukocytes, and the latter merge with areas of necrosis in which alveolar walls, blood vessels, and small bronchi are mere shadows and the alveolar and bronchial exudate has been transformed into a granular formless necrotic mass (Fig. 167). In some cases, stainable tubercle bacilli are numerous in the caseous areas, but not in all. Usually, acid-fast bacilli are few in the gelatinous exudate. When softening occurs in the zone around a small or medium-sized bronchus, bacilli are usually found in large numbers but only after partial evacuation of the softened material has occurred. Openings, which on macroscopic examination appeared as dilated bronchi, are seen in microscopic preparations to be small cavities, lined by caseous membranes from which all details of structure have disappeared, and surrounded by densely consolidated parenchyma ("caseous bronchopneumonia") (Fig. 167). Thus, it is clear that, in view of its mechanism of development, all tuberculous pneumonia is bronchogenic in origin. Since the large quantities of tubercle bacilli or tuberculoprotein necessary to bring about a rapid spread of tuberculous inflammation are rarely, if ever, introduced at any one time into human lungs from the outside, the process is usually initiated by antigen derived from a rapidly disintegrating lesion in the subject's own lung. Tuberculous pneumonia is observed most often in association with necrotic, excavating lesions of the upper lobes in chronic fibrocaseous tuberculosis of adults but sometimes occurs in progressive primary infections.

MILIARY TUBERCULOSIS

Too often the idea is implied, if not expressed, that the escape of living tubercle bacilli into the blood stream inevitably leads to miliary tuberculosis. Even in the relatively susceptible infant this is not necessarily the case, and at all other ages it is certainly the exception rather than the rule. A few bacilli make their escape intermittently from all active lesions, some in the lymph, some through walls of capillaries and venules which lie within the areas of active infection, and some by erosion of tubercles in the intima of

large veins. Less commonly, caseous lymph nodes or parenchymal nodules which lie against the walls of large vessels enlarge so that the caseous process extends directly through the wall and becomes eroded on the intimal surface. Most of the tubercle bacilli escaping in the lymph are arrested in the lymph nodes. Some reach the right lymphatic duct or thoracic duct and are spilled into one of the subclavian veins. Those carried by the blood stream are taken out rapidly by the phagocytes of the spleen, liver, bone marrow, and other tissues. If in very small numbers, intracellular destruction may take place without the formation of recognizable lesions. In the presence of larger numbers, the macrophages are stimulated to form small compact aggregates, with or without the formation of giant cells. These disintegrate and disappear after the destruction of the bacilli. Little or no caseation occurs in the smallest of the epithelioid cell tubercles (Fig. 159, right). An occasional focus of larger size may result from the lodgment of a larger bacterial embolus, but even these, in the resistant individual, usually become arrested and encapsulated after a phase of progressive enlargement and caseation (Fig. 159, left). Such occasional foci, more or less accidentally initiated, do not constitute the entity of miliary tuberculosis in the usual sense of the term. The latter merely exhibits a much greater number of lesions with greater uniformity of distribution and size.

By definition, the lesions of miliary tuberculosis are numerous and small, varying upward and downward from a millimeter in diameter (millet-seed-sized). In the adult as in the child, the lesions usually are most abundant in the lungs where conditions are best for their development and quite evenly spaced in the parenchyma, but appear in especially large numbers in the pleura and subpleural parenchyma. Within the lung, the tubercles have a tendency to show slightly larger size and closer spacing in the upper lobes and progressively fewer nodules as the base is approached, but no part is spared. The nodules form chiefly within alveolar walls and septa where the bacterial emboli are filtered out of the blood. Since bacilli in each

minute foci are few, evidence of necrosis is slight in the early stage of their development. As the foci enlarge by the accretion of large mononuclear cells at the periphery, they become more spherical, central caseation occurs, multinuclear giant cells are formed, and proliferation of fibroblasts at the periphery furnishes a more or less well-defined capsule if the individual survives for a sufficiently long time (Figs. 158 and 159).

tubercles are relatively few and usually small. They tend to occur most frequently in the cortex and especially in the subcapsular zone. They are most readily identified by microscopic examination of multiple sections but can be made more easily visible to the unaided eye by allowing the capsular surface to dry slightly in the air after stripping the capsule of the fresh organ. In their earliest (epithelioid cell) stages they appear as poorly defined,



Fig. 169.—Hematogenous tuberculosis of the lung. Note uniform distribution of tubercles throughout the parenchyma. The subpleural tubercles are obscured by fibrinous exudate on the pleural surface.

The other organs are not spared, but tubercles may be small and few by comparison with those in the lungs. In the liver and spleen (Fig. 159), microscopic examination may be necessary for their identification, especially in the commonly observed cases of chronic progressive tuberculosis where miliary tuberculosis is merely a terminal event. In the kidneys,

faint gray spots on the red surface and as discrete, elevated spherical nodules in the older, encapsulated forms. In organs such as the liver and spleen, miliary tuberculosis in a normally resistant white adult is not, of itself, a serious event because of the tendency for regression to occur. In the meninges it is usually a fatal complication, but, even here, completely

healed tubercles in fairly large numbers are occasionally found. Numerous healed miliary tubercles in the lungs are far from rare.

EXTRAPULMONARY TUBERCULOSIS

Up to this point little has been said about tuberculous lesions outside of the lungs, partly because the principles of tuberculous infection are best illustrated by descriptions of the process in the lung and partly because in man pulmonary infections are overwhelmingly the most important in frequency of occurrence and from the standpoint of prevention and therapy. With

involvement is frequent. The smallest lesions usually regress, however, and, as a rule, progressive destructive lesions are confined to one side. It is for this reason that surgical removal of a grossly infected kidney is often followed by recovery. The disease is the result of progressive extension of a cortical or medullary tubercle or group of tubercles which coalesce and extend toward the pelvis (Fig. 171). Secondary caseous lesions form in the papillae, undermine the epithelium of the calyces, and lead to necrosis and ulceration in the pelvis, extending into ureters and mucosa of the urinary bladder where tubercles first appear around a ureteral orifice. The renal lesion may, after a period of extension,

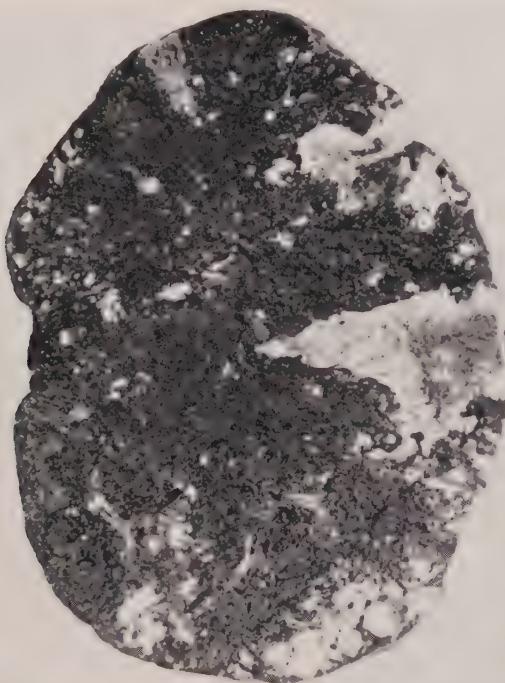


Fig. 170.—Caseous tuberculosis of the spleen. In the middle one-third, the lesion takes the form of an infarct ("caseous infarct").

some exceptions, there is a pronounced tendency for extrapulmonary lesions to heal spontaneously so that it is common practice to institute suitable procedures to promote healing of the pulmonary lesions and allow the extrapulmonary foci to heal spontaneously without special therapy. Important exceptions to this are progressive lesions in the kidney (see page 583) and those in bone (see page 1206). Less common are destructive caseous lesions of epididymis, fallopian tubes, adrenal glands, and brain, any of which may occasionally continue to progress long after the pulmonary infections have become inactive.

Renal Tuberculosis.—Infection of the kidney is usually blood-borne, and bilateral in-

gress and heal by fibrosis, but the percentage of spontaneous cures is probably small. After reaching a stage which is recognizable clinically, renal infections usually progress slowly to form extensive caseous lesions and ultimately to the complete destruction of the kidney. Softening of the caseous masses in the medulla is followed by the formation of cavities which communicate by wide orifices with the pelvic cavity. The cavities commonly are lined by a broad zone of unliquefied caseous substance and surrounded by a common capsule of dense scar tissue and atrophic renal parenchyma. Between the necrotic membrane and the fibrous capsule, a poorly defined zone of granulation tissue containing tubercles in various stages of develop-

ment can be distinguished. In other portions of the kidney may be found large masses of caseous substance which have become completely encapsulated, have encroached upon the pelvis, but have not ulcerated. On macroscopic inspection these resemble very closely the lesions of chronic pyogenic abscess and are somewhat inaccurately designated as "tuberculous pyonephrosis." In the earlier stages, the upper poles of the kidneys are involved more frequently than are the mid-portions or lower poles (see also page 583).

Fig. 171.



Fig. 172.

Fig. 171.—Tuberculosis of the kidney. Clusters of tubercles are located in the parenchyma of the upper one-third and the upper calyces are principally involved by necrosis and ulceration. The lining of the pelvis and ureter is diffusely thickened and irregularly nodular.

Fig. 172.—Caseous tuberculosis of the prostate gland.

Tuberculosis of Bones and Joints.—Although inconsequential foci of infection are probably formed and resolved in the marrow during the active stages of many cases of pulmonary tuberculosis, clinically recognizable infections are mainly confined to children between the ages of 5 and 15 years. Foci of progressive tuberculosis of bone arise as a part of the early hematogenous dissemination during the active stages of primary lesions. In the United States, the great majority are secondary to pulmonary foci caused by human-type bacilli. Even in Scotland where the incidence of bovine infections is high, less than one-half of cases of bone and joint tuberculosis are caused by bovine-type bacilli.⁶ The cancellous portions of bone which contain red marrow are the sites of predilection. Vertebral bodies and discs, ends of the long bones at the hip and knee, the humerus, and the bones of hands and feet are most frequently affected. The lesions form in the marrow, replace it with granulation tissue, and destroy bony trabeculae by slow absorption. Extensions toward the joint result in the undermining of articular cartilages and subsequent infection of the synovial membranes. The latter may be infected directly through the blood stream, but this occurrence, in the absence of osseous infection, is uncommon. Typical epithelioid cell tubercles with Langhans giant cells are found in synovial membranes and periarticular tissue, but well-defined tubercles in the substance of the bone are rare. Usually the microscopic recognition must depend upon the finding of scattered small fragments of dead cancellous bone ("caries"), replacement of marrow by granulation tissue or fibrous tissue, poorly defined areas of caseous necrosis within the masses of granulation tissue, and occasional multinucleated giant cells. It is frequently difficult or impossible to demonstrate the presence of acid-fast bacilli in the lesions of bone (see also page 1206).

Tuberculosis of Central Nervous System.—Few cases of fatal pulmonary tuberculosis in adults show, at necropsy, an important degree of involvement of the brain, spinal cord, or meninges. Minute tubercles are occasionally discovered as a part of generalized miliary tuberculosis, but generally these are far fewer in the meninges than in thoracic and abdominal viscera. In children, on the other hand, tuberculosis of the brain and meninges is one of the important causes of death. The two characteristic forms are tuberculoma of the brain and tuberculous leptomeningitis. Infection takes place through the blood in all except rare cases in which direct extensions to the meninges follow tuberculosis of the spine or skull.

Tuberculoma of the brain occurs as solitary or multiple lesions varying from a few millimeters to a few centimeters in diameter. Individual lesions are irregular in shape, often roughly spherical, and, in long-standing foci, may show well-formed capsules (Fig. 173). As space-occupying lesions, they produce various neurological signs, depending upon their location, size, and rate of enlargement. Some become permanently arrested, but many times they extend slowly until they reach the ventricles or leptomeninges and give rise to meningitis.

Histologically the centers are structureless, necrotic areas, less dense than caseous tubercles formed in lung or lymph nodes. The borders are composed of cellular connective tissue within which are lymphocytes, epithelioid histiocytes, and occasional Langhans giant cells. The adjacent brain substance shows edema and increased number of glial cells.

Tuberculous leptomeningitis is the result of liberation into the cerebrospinal fluid of large quantities of tubercle bacilli or their products from a necrotic focus in brain substance, choroid plexus, or leptomeninges. The focus is usually a small solitary caseous focus adjacent to the wall of the ventricle or a caseous plaque in the meninges. Rich and McCordock⁴⁴ were able, by careful dissection, to demonstrate such a focus in almost every case of tuberculous

scure by the superimposed exudate. From the region of the caseous focus, the exudate spreads in all directions, but accumulates particularly at the base, and then extends upward over the convexity, especially in the Sylvian fissures. In most cases the exudate in fissures and sulci is sufficient only to produce a milky opacity. Discrete tubercles are few, if distinguishable at all, and often confined to the deep recesses of the fissures of Sylvius. In microscopic sections, the most characteristic finding is the presence of thick mantles of exudate around the small meningeal vessels. Fibrin is abundant and enmeshes monocytes, polymorphonuclear cells, and lymphocytes. Poorly defined but extensive areas of necrosis are usually present in the denser masses of exudate, centering about the blood vessels. Acid-fast bacilli are demonstrable in



Fig. 173.—Large semicaseous tuberculoma of the inferior portion of the left hemisphere (11-year-old child); tuberculous leptomeningitis. The subarachnoid space, especially around the brain stem, is diffusely infiltrated with exudate.

meningitis, but several other investigators have failed to confirm these findings. The results of animal experiments designed to clarify this question, appear to substantiate the conclusions of Rich and McCordock. In previously hypersensitive animals, injection of suspensions of bacilli into the carotid artery is not followed by the development of tuberculous meningitis because relatively few bacilli are arrested by the small vessels of the pia-arachnoid, but if injections are made directly into the subarachnoid space the exudative reaction ensues rapidly. When the quantities of bacilli, reaching the meninges even of the hypersensitive animal are small, they are capable of exciting only local tubercle formation, and not the vigorous exudative reaction characteristic of tuberculous meningitis.⁴⁴ In human cases, the focus may be small and difficult to find because ob-

the exudate. Discrete epithelioid cell tubercles and multinuclear giant cells are not present as a part of the exudative meningitis in rapidly fatal infections but may be found as part of a coexistent generalized miliary tuberculosis. In the more prolonged course, caseous tubercles with characteristic cellular reactions are formed, and rare cases of completely arrested lesions have been observed in adults (see also page 1327).

Tuberculosis of the Genital Organs.—Of the male genital organs, the prostate gland is most frequently involved. With rare exceptions, the process is initiated by blood-borne bacilli. Interstitial tubercles enlarge, extend into the lumen of glands, and ultimately convert much of the gland into a fibrocaseous mass (Fig. 172). The seminal vesicles may be involved either by extension from prostatic infection or by the

hematogenous route. Their walls become thick, fibrous, and eventually caseous. The entire lumen may become filled with cheesy matter. There is little evidence that the epididymis is often infected by retrograde extension along the vas deferens, and the evidence is heavily weighted in favor of hematogenous infection, beginning as interstitial tubercles and progressing by direct extension to involve the rete testis, the testicular parenchyma, the tunica vaginalis, and the spermatic cord. The common appearance in the surgically removed or necropsy specimen is that of an enlarged epididymis with cartilage-like induration of its stroma and various degrees of caseous necrosis. Through the rete testis and the testicular parenchyma there are often seen cordlike extensions or isolated tubercles of more recent origin, consisting mainly of proliferative masses, obviously derived from the older process in the epididymis and rarely involving a large proportion of the testis. (See also page 633.)

Tuberculosis of the fallopian tubes arises as hematogenous tubercles in the mucosa and is usually bilateral. Extensions through the mucosa convert it into granulomatous and then into caseous masses, ultimately obstructing the lumen in the isthmic portion and at the fimbrial ostium. The serosa becomes thickened and may be studded with gray tubercles of various sizes. The common nonspecific inflammatory cysts of the serosa are frequently mistaken for miliary tubercles by the inexperienced. Orthograde extension from tube to endometrium takes place in a large proportion of infections during the active stages, but endometrial tuberculosis tends to heal when the immediate source of infection is eliminated by isthmic obstruction or by surgical removal of the fallopian tubes. Infection of the peritoneum through the fimbrial ostium leads to localized pelvic or generalized peritonitis.

References

- Holmes, W. H.: *Bacillary and Rickettsial Infections*, New York, 1940, The Macmillan Co.
- Long, Esmond R.: *Am. Rev. Tuberc.* **36**: 1-7, 1937.
- Halpin, E. H., and Turner, O. D.: *Pub. Health Rep.* **66**: 547, 1951.
- Dempsey, M.: *Tuberc. Abstr. N. T. A.* **24**: 1 (No. 4), 1951.
- Edwards, H. R., and Drolet, G. J.: *Am. Rev. Tuberc.* **61**: 39, 1950.
- Griffith, A. S., and Munro, W. T.: *J. Path. & Bact.* **35**: 271, 1932.
- Park, W. H., Krumwiede, C. J., et al.: *J. Med. Res.* **23**: 205, 1910.
- Feldman, W. H.: *Avian Tuberculosis Infections*, Baltimore, 1938, Williams & Wilkins Co.
- Rich, A. R.: *The Pathogenesis of Tuberculosis*, Springfield, Ill., 1944, Charles C Thomas.
- Anderson, R. J.: *Physiol. Rev.* **12**: 166, 1932.
- Heidelberger, M., and Menzel, A. E. O.: *J. Biol. Chem.* **104**: 655, 1934.
- Long, E. R., and Seibert, F. B.: *Am. Rev. Tuberc.* **13**: 448, 453, 1926.
- Seibert, F. B.: *Am. Rev. Tuberc.* **44**: 1, 1941.
- Sabin, F. R.: *Am. Rev. Tuberc.* **44**: 415, 1941.
- Seibert, F. B.: *Proc. Soc. Exper. Biol. & Med.* **30**: 1274, 1933.
- Anderson, R. J.: *J. Biol. Chem.* **83**: 505, 1929.
- Seibert, F. B., Pedersen, K. O., and Tiselius, A.: *Am. Rev. Tuberc.* **38**: 399, 1938.
- Moorman, L. J.: *Am. Rev. Tuberc.* **61**: 586, 1950.
- Pinner, M., and Kasper, J. A.: *Am. Rev. Tuberc.* **26**: 463, 1932.
- Terplan, K.: *Am. Rev. Tuberc. (suppl.)* **42**: 1, 1940.
- Long, E. R.: *Arch. Path.* **28**: 719, 1939.
- Weiss, C., and Halliday, W.: *Proc. Soc. Exper. Biol. & Med.* **57**: 299, 1944.
- Opie, E. L., and Barker, B. I.: *J. Exper. Med.* **9**: 207, 1907.
- Mills, M. A., Barth, E. E., and Gunn, F. D.: *Am. Rev. Tuberc.* **42**: 28, 1940.
- Gunn, F. D., and Sheehy, J. J.: *Am. Rev. Tuberc.* **61**: 77, 1950.
- Follis, R. H.: *Bull. Johns Hopkins Hosp.* **63**: 283, 1938.
- Gomori, G.: *Am. J. Path.* **19**: 197, 1943.
- Calmette, A., Guérin, C., Boquet, A., and Nègre, L.: *La vaccination préventive contre la tuberculose par le BCG*, Paris, 1927, Masson et Cie.
- Weill-Hallé, B., and Turpin, R.: *Bull. et mém. Soc. méd. de l'hôp. de Paris* **49**: 1589, 1925.
- Park, W. H., Keresztsuri, C., and Mishulow, L.: *J. A. M. A.* **101**: 1619, 1933.
- Rosenthal, S. R., Leslie, E. L., and Loewinson, E.: *J. A. M. A.* **136**: 73, 1948.
- Aronson, J. D., and Palmer, C. E.: *Pub. Health Rep.* **61**: 802, 1946.
- Clawson, B. J.: *Arch. Path.* **20**: 343, 1935.
- Rich, A. R., and McCordock, H. A.: *Bull. Johns Hopkins Hosp.* **44**: 273, 1929.
- Rich, A. R., Jennings, F. B., Jr., and Downing, L. M.: *Bull. Johns Hopkins Hosp.* **53**: 172, 1933.
- Sabin, F. R., and Joyner, A. L.: *J. Exper. Med.* **68**: 659, 1938.
- Martin, A. R., and Stewart, G. T.: *Brit. J. Exper. Path.* **31**: 189, 1950.
- Mahon, H. W.: *Am. Rev. Tuberc.* **61**: 543, 1950.
- Silverthorne, M. C., and Silverman, G.: *Am. Rev. Tuberc.* **61**: 525, 1950.
- Adams, W. E., and Vorwald, A. J.: *J. Thoracic Surg.* **3**: 633, 1933-1934.
- Feldman, W. H., and Baggenstoss, A. H.: *Am. J. Path.* **14**: 473, 1938.
- Sweany, H. C.: *Age Morphology of Primary Tubercles*, Springfield, Ill., 1941, Charles C Thomas.
- Reichle, H. S.: *Arch. Path.* **25**: 811, 1938.
- Brock, R. C., Hodgkiss, F., and Jones, H. O.: *Guy's Hosp. Rep.* **91**: 131, 1942.
- Terplan, K.: *Am. Rev. Tuberc.* **51**: 133, 1945.
- Rich, A. R., and McCordock, H. A.: *Bull. Johns Hopkins Hosp.* **52**: 5, 1933.

Chapter 12

LEPROSY

ENRIQUE KOPPISCH

Etiology

Mycobacterium leprae is a pleomorphic, acid-fast bacillus closely resembling *Myco. tuberculosis*, and measuring 1 to 6 micra in length by 0.2 to 0.5 in thickness. It may occur in irregular, coccoid or granular form, and may be nonacid-fast during a lepra reaction. While at times it stains evenly by the Ziehl-Neelsen method, at other times it is beaded, monopolar or bipolar, particularly in the more active lesions, and can be decolorized much more easily than the tubercle bacillus. In tissues and smears it forms clumps resembling cigar packs. Although discovered by Hansen as far back as 1874, it has proved insusceptible of cultivation, and its inoculation does not reproduce the disease in any experimental animal. However, there have been two or three cases suggestive of its successful inoculation to man. A very similar, acid-fast bacillus, *Mycobacterium leprae murium*, is constantly associated with rat leprosy, the lesions of which, histologically, are remarkably like those of the lepromatous form of the human disease, and which can be transmitted from rat to rat by experimental inoculation. As far as is known, the human and murine diseases are totally unrelated.

Epidemiology

Leprosy is a cosmopolitan malady that once was very common in northerly latitudes but which in the course of the last three or four centuries has become increasingly confined to the tropics. Most probably, this has not been the result of climatic influences, but of the more strict isolation of lepers in northern countries and of the presence in the tropics of conditions favoring the propagation of the infection, such as greater poverty, poorer personal and general hygiene, malnutrition, overcrowding, and more intimate contacts within the family. Even in endemic regions, leprosy is rare among the well-to-do and educated classes. While Central Africa, the Far East, and certain islands of the Pacific are the great endemic foci, the disease is fairly common throughout tropical and subtropical regions of both hemispheres, and still smoulders in several temperate regions. In the United States there are about 400 known lepers, most of them from the states bordering the Gulf of Mexico. Estimates from the whole world vary from 3,000,000 to 5,000,000 lepers.

The mode of transmission remains undemonstrated, but the most probable portals of entry are the skin and nasal mucosa, present knowledge definitely favoring the former. The disease is generally contracted during childhood or in youth, and it seems that in most cases prolonged

and intimate contact with an infective case is necessary. The possibility of transmission by some insect, although experimentally unproved, is still worthy of consideration. The disease usually has its onset before the age of 40, and is twice as common in males as in females. The incubation period averages five to ten years, but may be as short as three months in very young children, while in some adults it may have been twenty to thirty years.

Classification

Leprosy is a chronic granulomatous disease affecting mostly the skin, peripheral nerves, nasal mucosa, and lymph nodes. Depending on the patient's powers of resistance, on the duration of the illness, and on factors still unknown, there is wide variability as to the parts of the body that are predominantly affected, the histologic type of response to the lepra bacillus, the number of bacilli present in the lesions, and the course. The cutaneous lesions may be extremely varied in their aspect and evolution, both in the same case and in different cases. Besides the difficulties of classification inherent in the complexities of the clinical manifestations in some cases, there is much confusion due to the terminology, and resulting from the intermingling of clinical, dermatologic, anatomic, and pathologic concepts in the naming of lesions and of types of the disease. In the following brief definition of terms, the concepts of classification adopted by the International Congresses of Leprosy held at Cairo in 1938 (*q.v.*), and Havana in 1948, will be explained in terms of each other.

Lepromatous leprosy has been variously known as tuberous, tubercular, nodular, malignant, and cutaneous leprosy. This type is characterized by the formation of projecting nodules and diffuse infiltrations in the skin, composed of histiocytes (lepra cells) laden with bacilli, and by the infiltration of regional lymph nodes, the nasal mucosa, and peripheral nerves with lepra cells; in late cases, internal lymph nodes and certain viscera may also be involved. The course is relatively short, usually not over ten years. Most cases are infective, there being large numbers of lepra bacilli in the nasal mucosa, in the open skin lesions, and even in the intact epidermis over nodules and infiltrations. The lepromin or Mitsuda reaction, a skin test carried out with a suspension of lepromatous tissue rich in heat-killed bacilli, is negative or weakly positive, indicating little or no resistance to the infection. The sedimentation rate of erythrocytes is increased. Manifestations of involvement of peripheral nerves are present in

most cases, especially late in the disease. All leprologists agree in designating this type as lepromatous leprosy.



Fig. 174.—Lepromatous leprosy. A typical well-advanced case with leonine facies and multiple nodules and infiltrations of skin.

Tuberculoid leprosy is also referred to as neural, macular, anesthetic, maculo-anesthetic, or benign leprosy. It is characterized by very prominent signs of involvement of peripheral nerves, such as palpable thickening, sensory disturbances, muscle palsies and atrophies, contractures, and trophic changes, as well as by the appearance of macular, more or less infiltrated, or finely papular, anesthetic skin lesions. Histologically, tubercle-like nodules develop in the derma and peripheral nerves. Lepra bacilli are difficult to find in the lesions, or altogether undemonstrable. The course is prolonged and benign, often extending to over twenty years; many cases become arrested. Most patients are not infective. The lepromin reaction is usually strongly positive, indicating good resistance. The sedimentation rate is low.

Indeterminate leprosy is the newly adopted term for a group of cases with clinical manifestations mainly in skin and nerves. The cutaneous lesions are usually represented by flat macules, more or less sharply circumscribed, which may be hypochromic and erythematous or erythematous and dyschromic. Histologically the alterations are banal and not specific, consisting only of perivascular infiltration with lymphocytes and plasma cells. Lepra bacilli are generally undemonstrable in the lesions, or very scanty. The disease may persist in the above form, regress, or progress as either lepromatous

or tuberculoid leprosy. Cases with involvement of nerves may present thickening of these structures, cutaneous zones of anesthesia, muscular atrophy, and trophic alterations. The lepromin reaction, usually negative, may be moderately positive.

Pathogenesis and Pathologic Anatomy

Lepromatous Leprosy.—This form at times begins with one or more febrile attacks, after which a macular exanthem may appear, to be followed by the development of achromic, dyschromic, or hyperpigmented patches and, still later, by nodules and diffuse infiltrations of the skin. It may also begin directly with the appearance of nodular skin lesions of which, at first, there may be only one. The nodules vary from a few millimeters to about 3 cm. in diameter. The overlying epidermis is thin, smooth, and oily. They develop more frequently on the face, extensor surfaces of the extremities, and buttocks. The diffuse infiltrations may appear in various parts, but show a preference for the superciliary ridges, forehead, malar prominences, nose, and lips; this imparts to the face a highly characteristic leonine look. A diffuse erythema is often present over the affected parts, which

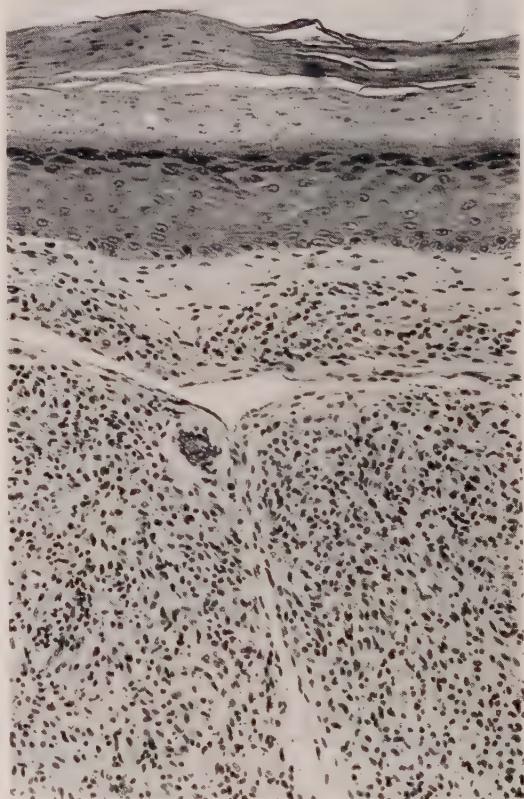


Fig. 175.—Lepromatous leprosy. Diffuse infiltration of derma with lepra cells. A narrow uninvolved zone often remains beneath the epidermis. ($\times 80$.)

may later become hyperpigmented, and from which the hair is usually lost. Lepromatous lesions tend to be bilateral and more or less symmetrical in distribution, and to show a diminution or absence of perspiration; usually, they are anesthetic. Adjacent nodules may coalesce. Some ulcerate, while others are absorbed, or undergo scarring, as new ones appear.

The cut surface of early nodules and infiltrations is yellowish or pale gray, while older ones are darker and brownish. Microscopically, there is an enlargement and multiplication of histiocytes in the derma (Fig. 175) and superficial parts of the subcutaneous fatty tissue. These are known as *lepra cells* and, when their cytoplasm is vacuolated, as *Virchow cells*; they have an oval, at times indented, vesicular nucleus, and many of them are laden with bacilli. At first the lepra cells are found mostly about sweat and sebaceous glands, hair follicles, and blood vessels, but the infiltration later becomes massive, with atrophy of skin appendages.

or later, but the enlargement is only moderate. They are soft and discrete, showing on section pale yellow or grayish homogeneous cut surfaces. Beginning in the cortex, and later extending centrally, there takes place a histiocytic proliferation, with the formation of lepra cells containing bacilli. In addition, there are globi and occasional giant cells, while plasma cells appear among the lymphocytes and histiocytes.

The involvement of *peripheral nerves* can be detected more frequently, by clinical examination, in the ulnar, great occipital, peroneal, facial, and supraorbital nerves. They undergo varying degrees of thickening, which may be diffuse, or fusiform and beaded. On section the nerves are pinkish-gray. Lepra cells appear among the nerve bundles, but do not form compact accumulations as in other lepromatous lesions. They are accompanied by a lymphocytic and plasma-cell infiltration of the perineurium, later extending to the endoneurium, along the blood vessels. The cellular infiltration compresses the

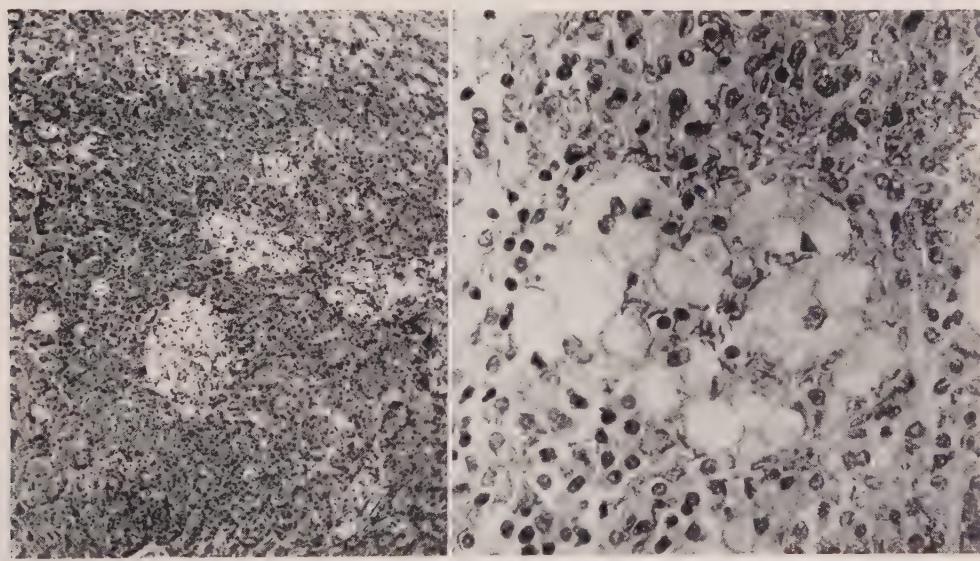


Fig. 176.—A, Lepromatous leprosy. Miliary lepromata in liver, composed of vacuolated histiocytes, often containing lepra bacilli. ($\times 80$.) B, Same as A, $\times 360$.

There generally remains a thin, uninvolved zone immediately beneath the atrophied epidermis. The microscopic groups of lepra cells, and their larger nodular conglomerations, are known as *lepromata*, which constitute the basic pathologic lesion of this type of leprosy. The lepra cells are accompanied by variable numbers of lymphocytes and plasma cells; rudimentary giant cells may also form, and globi are usually present. The latter are rounded or sausage-shaped compact masses of lepra bacilli in the center of vacuoles or spaces that measure up to 100 micra in diameter, and which have been variously interpreted as representing vacuoles within giant cells or lymphatic spaces (Cowdry, 1940).

The lymph nodes draining the affected cutaneous areas never fail to become involved, sooner

nerve fibrillae, thus producing a degeneration of the myelin sheaths and axis cylinders. The ultimate result is extensive scarring. These alterations explain some of the neurologic manifestations of lepromatous leprosy, but anesthesia may also be partly due to destruction of terminal filaments in the skin by the lepromatous infiltrations in the latter. It appears that the primary changes are in the skin, from which the infection extends into the nerves.

Except for a case of leprous meningitis,² no leprosous lesions have been encountered in the *central nervous system*, although bacilli have been seen in isolated neurons of the spinal cord (anterior horn), in Purkinje cells and pia mater, as well as in the Gasserian and spinal ganglia.⁴

Trophic changes are an important sequel of nerve involvement. Deep and destructive indolent ulcers may form, usually in the extremities. The bones of the terminal phalanges of fingers and toes undergo atrophy and resorption, resulting in great shortening of the digits or, if this is complicated by the development of ulcers, there may be spontaneous amputation of digits and even of portions of the hands and feet, so that only stumps will remain.

Lepromatous infiltrations frequently develop in the *nasal mucous membrane*, usually in flat and diffuse fashion and, more rarely, as nodules.

are large, and often contain lepra bacilli. The *spleen* may also enlarge. Microscopically there is increased prominence of the reticulo-endothelial elements, in which bacilli may be found, and miliary lepromata develop in the red pulp. The latter may also form in the *bone marrow* and, rarely, in the *lungs*. The *gonads* are attacked in many cases, particularly in the male. There is interstitial infiltration of the *testis* with lepra cells laden with bacilli, which results in extensive scarring and testicular atrophy. Only a few cases of lepromatous involvement of the *ovaries* are known.



Fig. 177.—Tuberculoid leprosy. Typical anesthetic plaques in leg with slightly elevated and erythematous border.

There is superficial ulceration and crust formation, with partial obstruction of the nasal passages and with occasional epistaxis. The nasal septum is often destroyed. Because of the ease with which bacilli are often demonstrable in smears of nasal swabbings, this leprous rhinitis is of great practical importance in diagnosis, even in cases with no visible involvement of the nasal mucosa. In some advanced cases, the mucosa of the *epiglottis*, *larynx*, and upper portions of the *trachea* undergoes similar changes. This ultimately results in obstruction of the air passages from excessive infiltration of the mucous membrane by lepra cells, plasma cells, and lymphocytes, or secondary to cicatricial constrictions.

The liver and spleen are the *viscera* most frequently involved. Late in the course of the disease the *liver* is often enlarged, due to amyloidosis or, more frequently, to fatty change. At autopsy, minute pale yellow foci may be visible grossly in the parenchyma. These are the miliary lepromata, composed of vacuolated lepra cells, in which bacilli are usually demonstrable, and which apparently are derived from the Kupffer cells (Fig. 176). The latter



Fig. 178.—Claw-hands in tuberculoid leprosy.

The disease may extend to the *eyeball*, producing a leprous keratitis. Lepra cells may also appear in the *iris*, which fuses to the *cornea*, while the lens degenerates. After a time the ocular process may become quiescent, but by

this time the cornea is diffusely white (leukoma) from the scarring, and the eye is totally blind.

The pathologic lesions all appear to be instigated directly by the bacilli. While these are most abundant in lepra cells and globi, they may also occur in the following locations: sebaceous and sweat glands, corpuseles of Pacini and Meissner, hair follicles, swollen endothelial cells of lymphatic capillaries in lepromata, subcutaneous fat cells, free in the unaffected zone separating the lepromata from the

or with the development of macular skin lesions (Fig. 177). In its course, bullae may appear unexpectedly, singly or in groups, and at times in successive crops. They rupture after a few days, with the formation of superficial excoriations that encrust and heal, leaving rounded areas of anesthesia surrounded by hyperpigmented borders.

After a time, some of the peripheral nerves may become thickened and palpable. The thenar and hypothenar eminences and the interossei muscles undergo atrophy. Other muscles,

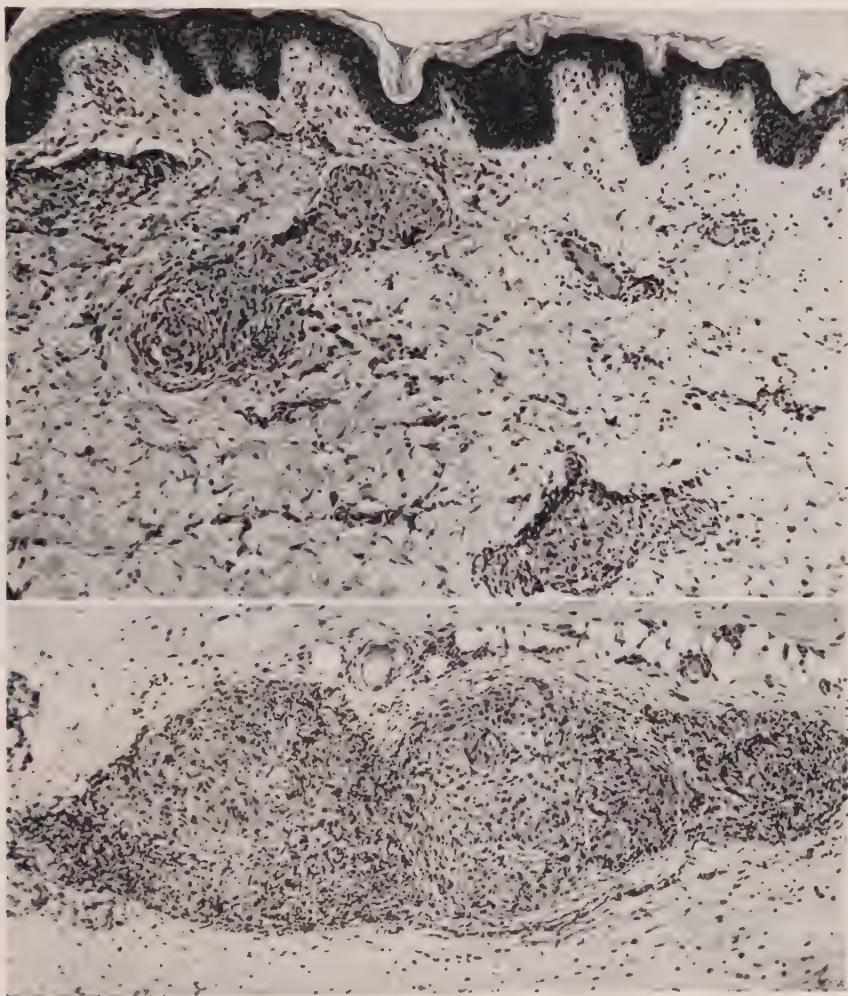


Fig. 179.—Tuberculoid leprosy. Focal groups of histiocytes admixed with lymphocytes in derma. Biopsy of erythematous border of an anesthetic plaque. ($\times 80$.) (Preparation of Dr. Francisco León Blanco, Havana, Cuba.)

epidermis, all layers of the epidermis, connective tissue of peripheral nerves, certain cells of the central nervous system mentioned above, placenta, and the blood.

Tuberculoid Leprosy.—This form may begin with fever, neuralgic pains, or sensory disturbances (formication, paresthesia, hyperesthesia),

such as those of the forearm, become markedly wasted, and contractures develop. In the hands this produces the characteristic *main en griffe* (Fig. 178). Trophic changes also appear, with the formation of abscesses and ulcers, particularly in the fingers, toes, hands, and feet, that result in gross mutilations. The atrophy

often involves the facial muscles, resulting in ptosis of the upper eyelids, ectropion, and ulceration of the cornea.

The well-developed *macule* of tuberculoid leprosy is circular, with the central parts paler than the remainder of the skin, and with a well-defined, erythematous, slightly elevated and indurated border that often is finely papular. Macules vary in diameter from small lesions of about 1 cm. to large ones involving extensive portions of the face, trunk, and limbs. The center usually is anesthetic. Microscopically the edges show the formation of tubercle-like groups of histiocytes in the derma, accompanied by Langhans giant cells and a slight diffuse infiltration with lymphocytes; there is no caseation (Fig. 179). In the center of macules the reaction usually consists of perivascular infiltration with lymphocytes and plasma cells.

grene, followed by deep ulcerations that may extend into muscles, tendons and joints, causing extensive mutilations, mostly in the extremities. There are numerous bacilli in the necrotic portions, even though the histologic type of reaction about the ulcers is tuberculoid. The lepromin test is strongly positive, and the prognosis is good, except for the mutilations and scarring. This form is thought to be a variant of tuberculoid leprosy.⁸

Lepra Reaction.—This is a peculiar, acute inflammatory episode, that may supervene at any time in the course of leprosy, and which is suggestive of hypersensitivity. In lepromatous leprosy the reaction is characterized by high fever, at times with prostration, by the appearance of an eruption like erythema multiforme or nodosum, and by an activation of all the pre-existing leprotic lesions. It lasts for one or two

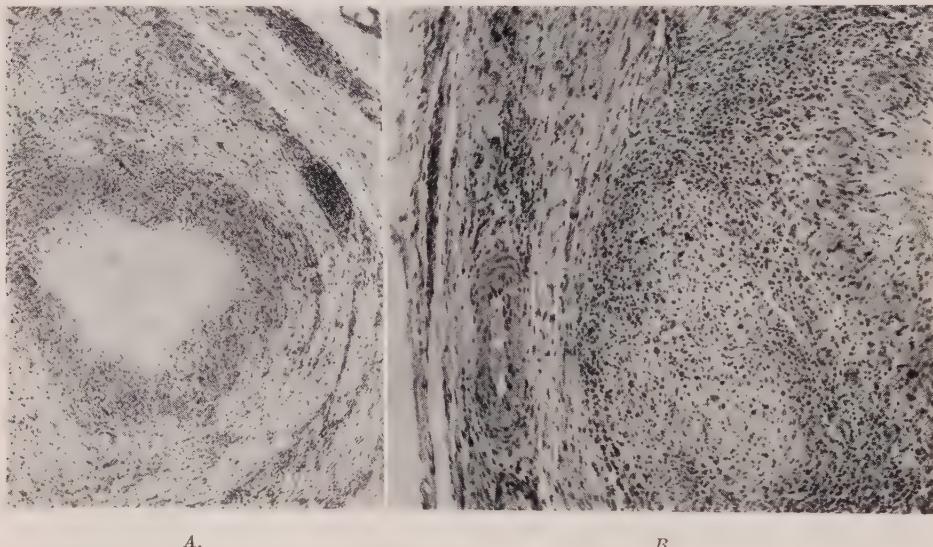


Fig. 180.—Tuberculoid leprosy. Early nerve abscess beginning as zone of coagulation necrosis surrounded by epithelioid cells. The rest of the nerve is markedly fibrosed. (A, $\times 40$. B, $\times 80$.) (Preparation of Dr. Francisco León Blanco, Havana, Cuba.)

The nerve trunks are affected in either diffuse fashion or in spindle-shaped, single or multiple areas. The histologic inflammatory response is of tuberculoid type, and there is a marked tendency to fibrosis, with extensive replacement of nerve fibrillae. At times, a localized enlargement in a nerve becomes very painful and goes on to softening, discharging a soft and whitish material through the skin. Microscopically, these so-called *nerve abscesses* present central caseation and softening, about which there is a zone of epithelioid cell reaction (Fig. 180).

Tuberculoid changes, indistinguishable from those of Boeck's sarcoid, have been described in lymph nodes. Bacilli are difficult to demonstrate in all lesions of tuberculoid leprosy.

Lazarine Leprosy.—This is a very rare form of leprosy in which the only manifestation of the disease consists in the appearance of successive crops of bullae that lead to the formation of cutaneous plaques of necrosis or gan-

weeks, and may be followed by improvement. In tuberculoid leprosy the reaction consists of an increased prominence of the skin lesions and of the appearance of dark red patches of infiltration, without fever. The reaction may last from three months to one year and is of good prognosis.

Complications

Complications occur mostly in lepromatous leprosy, the majority of cases of this type succumbing to one of them, rather than to leprosy itself. The more frequent ones are nephritis, tuberculosis, bronchopneumonia, acute bacterial endocarditis, and septicemia. Amyloid changes are often found in various viscera at autopsy.

Immunity

Since not all who are exposed to leprosy in childhood acquire the disease, there probably

exists in some individuals a natural resistance. The lesser incidence of the disease after the age of 40 suggests that there may develop an acquired immunity, or an age resistance. The three main types of histologic reaction (lepromatous, tuberculoid, and indeterminate) and the response to lepromin indicate different degrees of individual immunologic response to the lepro bacillus. Evidence has been collected to the effect that some persons have a hereditary familial predisposition to leprosy.

References

1. Arnold, H. L., and Tilden, I. L.: Ann. Int. Med. 23: 65, 1945 (classification and nomenclature).
2. de Beurmann, M., Gougerot, H., and Laroche, G.: Lepra 11: 177, 186, 1910.
3. Cowdry, E. V.: Am. J. Path. 16: 103, 1940 (globi).
4. Fite, G. L.: Arch. Path. 35: 611, 1943 (histology).
5. Mitsuda, K.: Internat. J. Leprosy 4: 491, 1936 (lepra cells).
6. Mitsuda, K., and Ogawa, M.: Internat. J. Leprosy 5: 53, 1937 (autopsy findings).
7. Oliver, J.: J. Exper. Med. 43: 233, 1926 (lepra cells).
8. Pardo-Castelló, V., and Caballero, G. M.: Arch. Dermat. & Syph. 23: 1, 1931 (lazarine leprosy).
9. Pardo-Castelló, V., and Tiant, F. R.: J. A. M. A. 121: 1264, 1943.
10. Rogers, L.: Internat. J. Leprosy 4: 469, 1936 (epidemiology).
11. Schujman, S.: Internat. J. Leprosy 5: 77, 1937 (tuberculoid leprosy).
12. Wade, H. W.: Internat. J. Leprosy 3: 121, 1935 (tuberculoid leprosy).
13. Reports of Meetings of the First International Congress on Leprosy: Internat. J. Leprosy 6: 389, 1938.

Chapter 13

SPIROCHETAL AND VENEREAL DISEASES

EDGAR R. PUND

SYPHILIS

Syphilis, because of its frequency, seriousness, and protean manifestations, is the most important of the venereal diseases. The origin of syphilis is controversial, but most evidence indicates that it was endemic in the Western Hemisphere in pre-Columbian times, and was disseminated in epidemic proportions by Columbus' sailors upon their return to Europe. Its spread to Europe and Asia was rapid, and the disease is now worldwide in distribution. Its incidence varies according to the degree of recognition and the access to medical care. In this country it is more common in Negroes than in white persons. In a series of autopsies on syphilitics, significant lesions have been found in 30 per cent, and in 20 per cent syphilis was the cause of death. Its variety of manifestations necessitates consideration of syphilis in the differential diagnosis of many symptom complexes. It was recognized as a distinctive disease apart from other venereal diseases by Ricord in 1831. The disease is frequently transmitted to the offspring, and transmission to the third generation has been observed. It is therefore divided into two forms, acquired and congenital.

Cause

The causative organism, a spirochete which is classified as a treponema, was discovered by Schaudinn in 1905. The *Treponema pallidum* (*Spirochaeta pallida*, *Borellia pallidum*) is 5 to 15 microns long and is characterized by its thinness and the closeness and regularity of its corkscrewlike spirals which average 12 in number. It is rapidly motile. It stains with great difficulty and is best demonstrated in films from syphilitic lesions by dark-field examination or against a dark background of India ink or nigrosin. In tissues it may be demonstrated by silver impregnation. The organism can be cultivated in tissue and the disease is easily transmitted to rabbits and monkeys. By using an extract of the liver from a syphilitic infant as an antigen, Wassermann developed a complement fixation test in 1906. It was soon found, however, that

the reaction was not dependent upon the presence of a large number of spirochetes and that extracts of heart muscle could be substituted. Beef hearts are now the usual source of antigen, and precipitation tests have also been developed. The complement fixation or precipitin test becomes positive ten to fifteen days after the development of the initial "sore." Immunity begins to develop upon the appearance of the chancre, but the spirochete carrier is immune to new infection only as long as he carries the spirochete.

General Pathology of Syphilitic Lesions

The specificity of the lesions of syphilis depends in large measure upon the demonstration of the spirochete. In the absence of spirochetes, the histologic changes are only suggestive and are interpreted from observations which have accumulated in the past and, in individual cases, from the clinical course and presence of a positive Wassermann or related test. Spirochetes are easily demonstrated in the early lesions but with difficulty in the late ones, with the exception of paresis. The usual inflammatory reaction is characterized by exudation, production, and degeneration. The characteristic cells of the exudate are plasma cells, lymphocytes, and macrophages, and there is always a tendency for the exudate to stream along the vessels. The inflammatory reaction will vary according to the number of organisms present, the duration of the inflammation, the site of the lesion, and the degree of immunity and sensitivity.

Frequently, spirochetes are universally numerous in the syphilitic fetus, and death may result from the overwhelming spirochetal dissemination with little inflammatory response. Because a large number of organisms are present in early focal lesions, exudation predominates; production is limited to slight fibroblastic activity and increased vascularization; and degeneration is minimal.

The essential pathologic change of the late and latent tertiary lesions is a mild

inflammatory reaction, with lymphocytic and plasma cell infiltration in the stroma, particularly about the blood vessels and lymphatics. There is slight tissue proliferation, with eventual fibrosis and progressive atrophy and degeneration of the parenchyma and specialized tissues. Proliferative obliterative endarteritis of small arteries also occurs. This reaction is due to localization in tissues of relatively avirulent organisms and to the development of an increasing degree of immunity which begins to develop upon the appearance of the chancre and increases during the secondary stage of the disease. Mesaortitis and syphilitic orchitis are examples of this type of reaction. Later, the degree of tissue immunity begins to fluctuate and diminish, and more active lesions develop which may be characterized by degeneration, an intense infiltrate, or both. The lesions of neurosyphilis illustrate this reaction and it is interesting to note that these lesions are more common in inadequately treated early syphilis than in the untreated cases, probably because the latter develop a more lasting immunity. Women, as a rule, receive treatment later than men because of the concealed primary, and neurosyphilis is less often encountered in women than in men.

The type of reaction also depends upon sensitization as well as immunity, and focal lesions with central necrosis (gummas) may occur. The reaction about the central area of necrosis is infiltrative and productive, and, in addition to the small round cells, large numbers of macrophages and occasional giant cells are observed in the exudate, and vascularized connective tissue proliferates.

Acquired Syphilis

Syphilis is usually acquired by sexual intercourse; hence the initial lesion is found most frequently on the genitals. Although abrasions facilitate their entrance, the spirochetes may penetrate the normal skin and mucous membranes. The most infectious lesions are the chancre and secondaries, particularly mucous patches, although the disease may be transmitted during the incubation period prior to the development of the chancre. Semen may be infectious as long as four years after the chancre, but most syphi-

lities do not transmit the disease after the second year. The causative organism rapidly dies when removed from living tissue and is readily killed by soap and water. A few innocent infections are acquired, in which the lip and finger are the usual sites of inoculation. Accidental infections may follow transfusion of blood from syphilitic donors.

The course of the disease is divided into three stages, primary, secondary, and tertiary. When the disease is transmitted by transfusion, the occurrence of secondary lesions is the first manifestation.

PRIMARY STAGE

Soon after exposure and prior to the development of the initial lesion, the chancre, the spirochetes penetrate the lymphatics and capillaries and are disseminated throughout the body. In rare instances a chancre may fail to develop and the disease may be first recognized in the secondary stage or, in the absence of secondaries, tertiary lesions may be the first clinical evidence of the disease. In the usual case, after an incubation period of approximately three weeks, the chancre develops at the site of inoculation, generally on the penis in the male and on the vulva or cervix in the female. It is, therefore, frequently a concealed lesion in the female. When the primary lesion occurs within the urethra of the male, it may escape detection or only be evident as a small area of induration which is accompanied by a seromucoid urethral discharge. A regional lymphadenopathy follows within a few days, and the nodes are painless, hard, slightly enlarged, and freely movable. Spirochetes are readily demonstrable in films from the chancre and in serum extracted from the lymph nodes.

Pathologic Anatomy of the Chancre.—The chancre is usually single but may occur as multiple lesions. It begins as a macule which soon develops into a painless indurated papule which may vary in size from a diameter of a few millimeters to several centimeters. The surface becomes eroded but the superficial ulceration rarely involves the entire surface of the elevated, circumscribed, indurated nodule. The characteristic chancre is, therefore, a superficially ulcerated button-



Fig. 181.—Spirochetes (*Treponema pallidum*) in a section from a mucous patch of vulva.

like lesion whose surface is covered with adherent fibrin. When the fibrin is removed from the round erosion, the surface appears red and smooth and the margin of the ulcer is flat and sharply delimited. The circumscribed induration extends beyond the margin of the erosion. Mixed infections, particularly concomitant infection with Durey's bacillus, alter the appearance of the chancre.

Histopathology of the Chancre.—The subepithelial tissues are densely infiltrated with lymphocytes, plasma cells, and a few macrophages. There is an associated capillary proliferation and slight fibroblastic activity. A few neutrophilic leukocytes are observed superficially in the area of ulceration. At the margins of the ulcer there is elongation of the rete pegs, and the intense inflammatory reaction extends beyond the area of ulceration. A perivascular lymphocytic and plasma cell infiltrate emanates from the sharply delimited area of denser infiltrate. Numerous spirochetes are easily demonstrated by silver impregnation in microscopic preparations. The inflammation gradually subsides and, even without treatment, the chancre heals in four to six weeks without or with a small scar.

SECONDARY STAGE

The secondary stage begins five to six weeks after the appearance of the chancre and is characterized by malaise, chilliness, headache, body pains, general lymphadenopathy, and anemia. Sore throat is common, the tonsils are frequently enlarged, and organisms may be demonstrated in films from the tonsils. A mucocutaneous eruption follows. In the skin this is macular, maculopapular, papular, or, rarely, pustular, and ulceration is unusual. Focal superficial ulcers, which are known as mucous patches, occur on the mucous membrane of the mouth, vulva, vagina, penis, and, rarely, on the conjunctiva and larynx. Large numbers of organisms may be found in films from these lesions. Flat, warty growths, condylomata lata, which affect the moist surface of the skin, especially around the genitals, are late secondary manifestations as are also indurated keratotic papules of the plantar and palmar surfaces. All signs and symptoms of the secondary stage subside spontaneously within a few weeks. In untreated patients, mucocutaneous relapses may occur for several months to three years, with manifestations which localize on the genitals, oral mucosa, palms, and soles.

An acute nephrotic state, which is thought to be of syphilitic nature, is rarely associated with secondary syphilis. This condition, which is characterized by oliguria, albuminuria, presence of urinary casts, depletion of serum albumin, and edema, clears rapidly and leaves no residua.

Histopathology of the Secondaries.—The inflammatory reaction in the skin and mucous membranes is similar to that which is observed in the chancre. The infiltrate of lymphocytes and plasma cells is not as dense, and therefore the perivascular distribution is more evident. There may be occasional collections of macrophages and, rarely, giant cells. There is slight fibroblastic reaction and increased vascularity. The hyperplasia of the epithelium and elongation of the rete pegs are slight in the macular lesions and reach the extreme in condylomata lata. The mucosal lesions are similar but, in addition, are characterized by superficial ulceration. In the pustular cuta-



PLATE II.—Syphilis. Above, Primary lesion of vulva (chancre). Below, Papulosquamous secondary lesions. (From Top, *Handbook of Communicable Diseases*, The C. V. Mosby Co. Reprinted from Therapeutic Notes through the courtesy of Parke, Davis & Company.)

neous syphilide, minute focal abscesses develop in the epidermis, but ulceration of the cutaneous lesions is rare. Endarteritis which is characterized by endothelial proliferation and intimal fibrosis may occur in the late secondaries.

The affected tonsils are enlarged and the normal architecture is disturbed by a diffuse infiltrate of plasma cells, numerous macrophages, and an occasional giant cell. There is slight capillary and fibroblastic proliferation. The histopathology of the moderately enlarged lymph nodes of the primary and secondary stage is one of diffuse hyperplasia which involves reticulo-endothelial cells, lymphocytes,

apparent. These may develop spontaneously, as in the event of gummas, or, as is more often the case, may represent a symptomatic stage of a smoldering inflammatory process within the internal organs. The basis of the late visceral manifestations is probably determined during the initial spirochetemia. It is the tertiary lesions which are responsible for the crippling, maiming, disfigurement, and disabling of the acquired syphilitic. From necropsies on known syphilitics, lesions have been found distributed as follows: cardiovascular, 83 per cent; central nervous system, 18 per cent; and liver, 8.5 per cent.



Fig. 182.—Section of condyloma latum.

and especially the cells of the germinal centers. The germinal centers may greatly enlarge and the histology of the nodes may be confused with that of giant follicular lymphoma. Fibroblastic activity occurs which leads to some scarring, and small shotty nodes are common residua of syphilis. Spirochetes are demonstrable in sections of all secondary lesions.

TERTIARY STAGE

After a period of latency of several years, tertiary manifestations may become

The Gumma.—The gumma is a focal nonsuppurative inflammatory process characterized by an area of central necrosis of a rubbery consistency and opaque appearance. Gummas are usually solitary but may be multiple and vary from microscopic size to a diameter of several centimeters. An element of localized allergy is probably a causative factor in their spontaneous development and in their destructive character. They may occur anywhere in the body, and therefore symptoms are topical. The common sites

of gummas are the cutaneous tissues, mucous membranes, liver, bones, and testes. The bones most commonly involved are the palate, vomer, tibia, clavicle, frontal, and parietal. A gumma near a surface may ulcerate and the necrotic tissue may be discharged. The palate and vomer are common sites of perforation. Gummas heal with absorption of the necrotic material and fibrous replacement. As the fibrous tissue contracts, distortion results. In the liver the scars produce an apparent lobation, hepar lobatum. Multiple gummas of the liver may cause sufficient scarring and contraction to be attended by symptoms and signs which are identical with those of Laennec's cirrhosis. Destruction of the nasal bones produces the characteristic saddle nose. In the central nervous system the signs and symptoms of gummas are those of tumors.

HISTOPATHOLOGY OF GUMMA.—The irregular necrotic center is eosinophilic and usually homogeneous; however, a few architectural shadows may remain. The caseous center is surrounded by actively proliferating vascularized connective tissue which is infiltrated with lymphocytes, plasma cells, macrophages, and an occasional multinucleated giant cell. New-formed capillaries, which are accompanied by fibroblasts, extend irregularly into the caseous center. The ever-present perivascular infiltrate extends centrifugally, and endarteritis is observed in the small arteries of the periphery. Satellite focal lesions are rarely found. Treponemas are demonstrated with difficulty in gummas.

Chronic Degenerative and Sclerosing Lesions of the Tertiary Stage.—Gummas, while not uncommon, are not the usual type of lesion of late or latent syphilis. The most frequent inflammatory reaction is a selective involvement of the perivascular stroma of various organs and is characterized by a lymphocytic, plasma cell, and macrophagic infiltrate, fibroblastic activity, obliterative endarteritis, and atrophy of the parenchyma and highly specialized tissues. The infiltrate, the fibrosis, the degeneration, and the arterial changes vary according to the degree of activity; infiltration and degeneration predominate in active lesions, and fibrosis is conspicuous in those of a more chronic nature. The cardiovascular and

central nervous systems are not only most commonly involved, but the lesions produce the most serious manifestations of acquired syphilis.

Cardiovascular Syphilis.—Gummas may affect the myocardium, aorta, and aortic valve, but the most prevalent lesion of syphilis of the cardiovascular system is mesaortitis with or without aortic valvulitis. Negroes are affected more frequently than white persons and males more often than females. The first part of the aorta is the usual site; however, similar changes may occur in the larger branches of the aorta and, rarely, in the pulmonary artery. The gross appearance of the aorta is characteristic. One or more wrinkled pearly patches of varying size up to several centimeters in diameter, are observed in the intima of the aorta. In the early phase the patches may not be well defined, but in later stages they are sharply delimited. The walls of the sinuses of Valsalva are rarely affected; however, the elevated ridges may encroach upon the orifices of the coronary arteries with resulting stenosis. On section, the intima of the aorta appears thickened and pearly in color, the adventitia is thickened and denser than normal, and the media is not well defined. When an aneurysm is present, these changes are noted at its orifice. The presence of atheroma may alter the appearance and the elevated plaques appear yellow; however, atherosclerotic changes are not as pronounced in the first portion of the aorta as in other portions.

Syphilitic mesaortitis is frequently complicated with a chronic aortic valvular endocarditis. The commissures of the valve are widened and thickened and appear as a wedge between the cusps. The cusps are thickened, especially along the free margin. The contracted cusps are held rigid by the rolled free margin and widened commissures, and stenosis and incompetence of the valve results. The left ventricle dilates and hypertrophies to compensate for the regurgitation and stenosis.

HISTOPATHOLOGY OF CARDIOVASCULAR SYPHILIS.—The increased thickness of the adventitia is due to an increase in the fibrous connective tissue. There is an infiltrate of plasma cells and lymphocytes around the vasa vasorum of the adventitia, and the intima of the vasa is thickened and the lumen narrowed. The perivascular infiltrate follows the capillaries into the outer two-thirds of the media, and the elastic tissue about the capillaries melts away and is replaced by fibrous connective tissue. Subendothelial fibrosis of the intima of the aorta occurs in the affected portion. The loss of elasticity of the media and the patchy fibrosis of the intima cause the wrinkled appearance and the pearly elevated plaques. Similar histologic changes are observed in the aortic valve. At the base of the valves there is perivascular infiltrate and fibrosis. Vascularization of the valve ensues and the infiltrate extends along the new vessels. Degeneration of elastic tissue is followed by fibrous replacement.

ANEURYSM.—Saccular aneurysms of the sigmoid portion of the aorta and of the larger branches of the arch are the result of syphilitic

mesaortitis in over 95 per cent of the cases. The vasa vasorum of the media extend more or less perpendicularly from the vessels of the adventitia; therefore, the areas of medial elastic degeneration are transversely disposed. The local loss of elasticity, because of the confluence of the transverse medial degenerative lesions, leads to the production of a gradually expanding saccular aneurysm.

SYPHILIS OF MUSCULAR ARTERIES.—The small muscular arteries are frequently the site of endothelial proliferation, intimal fibrosis, and narrowing of the lumen in tertiary lesions. There is also a perivascular infiltrate of lymphocytes and plasma cells. This reaction constitutes part of all tertiary manifestations and frequently contributes to the symptomatology. In the cerebral vessels, ischemia, local cerebral atrophy, and thromboses may occur. Coronary insufficiency may rarely be caused by this process, and in the lung Ayerza's disease may result.

MENINGOVASCULAR SYPHILIS.—The onset of symptoms may be acute and may resemble those of bacterial meningitis. Usually, however, the symptoms are mild and extend over a long period of time. Nocturnal headaches are common and there may be slight evidence of meningeal irritation. The meninges of the base of the brain are more severely affected and the intracranial portions of the cerebral nerves may be involved, and eighth nerve deafness, optic atrophy, and oculomotor and sixth nerve paralysis may result. Paresesthesia and muscular weakness may be caused from extension of the inflammatory process along the pial prolongations of the cord, and transverse myelitis may result. Vascular spasms may cause transient paralyses, and cerebral thromboses may lead to permanent cerebral damage. The leptomeninges are infiltrated with lymphocytes, plasma cells, and macrophages in varying amounts according to the degree of activity. Fibroblastic activity produces thickening and adhesions of the



Fig. 183.—Syphilitic mesaortitis and aortic valvular endocarditis.

Syphilis of the Central Nervous System.—Neurosyphilis occurs in 20 to 25 per cent of untreated cases. It is more common in males than females and in white persons than Negroes. Three forms of neurosyphilis are recognized, meningovascular syphilis, paresis, and tabes dorsalis. Combinations of these are frequent, and meningovascular manifestations are commonly observed in cases of paresis and tabes. (See also discussion on page 1327.)

meninges, and obliterative endarteritis of the small arteries is observed. These changes may extend into the pial prolongations of the brain and cord.

PARESIS.—Paresis, or general paralysis of the insane, is a progressive cerebral degeneration which is generally chronic, but may be acute. The usual symptoms are nervousness, sleeplessness, personality changes, memory defects, impaired judgment, slurred speech, and agitation. The cere-

bral degeneration may progress and insanity and spastic paralyses result.

The leptomeninges appear cloudy, and scattered milky spots are noted. The pia-arachnoid is frequently adherent to the underlying brain and results in tearing when removed. The brain is shrunken, the convolutions appear small and the sulci wide. The frontal lobes are first affected, next the parietal, and later the temporal. Degeneration of the precentral gyrus is attended by degeneration of the pyramidal tracts of the cord. There is a compensatory increase in the cerebrospinal fluid and the ventricles are dilated. Fine granulations are noted in the ependyma of the ventricles, especially in the floor of the fourth ventricle. The dura is frequently thickened and adherent to the calvarium, and hemorrhagic pachymeningitis interna may be a complication.

loss of myelin and replacement gliosis. The loss of myelin is best demonstrated by specially stained preparations in which the degenerated fibers fail to stain. The posterior roots and ganglia also appear shrunken, and there is pyknosis, granular degeneration, and disappearance of the neurones in the ganglia and degeneration of the fibers. The pia-arachnoid about the roots may be increased in thickness due to fibrosis. Similar degeneration may occur in the optic, acoustic, and trigeminal nerves. (See also page 1329.)

Other Tertiary Manifestations.—

EYE.—Tertiary changes in the eye occur in 5 per cent of late cases. Primary optic atrophy may occur; there is an infiltrate of lymphocytes and plasma cells distal to the chiasm, and the

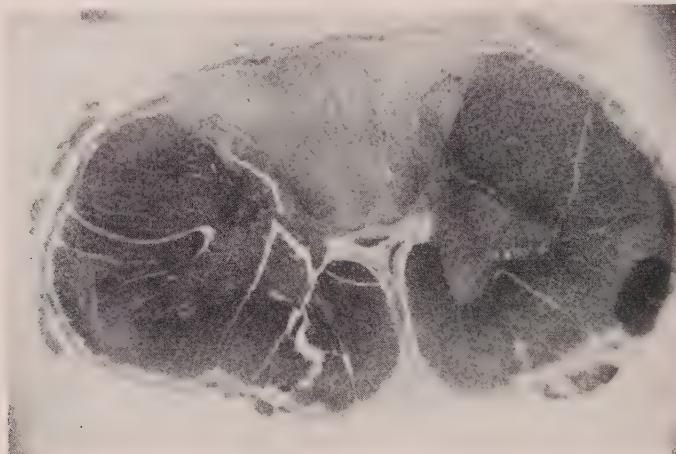


Fig. 184.—Section of cord from tabes dorsalis.

Microscopically there is a decrease in the number of cortical neurones, and in many of those remaining the nuclei are pyknotic. Glial cells are increased in number, the normal lamellation of the gray matter is obscured, and there is an increased vascularization. The cerebral degeneration is commonly associated with meningo-vascular changes. The ependymal granulations are due to subependymal focal glial proliferations which elevate and even disrupt the overlying ependyma. Spirochetes are usually demonstrable in sections in untreated cases, especially in the frontal lobe.

TABES DORSALIS (LOCOMOTOR ATAXIA).—Tabes dorsalis is a late manifestation of syphilis in which there is degeneration of the dorsal columns of the spinal cord, and it is frequently accompanied by degeneration of the dorsal roots. It occurs most commonly in the lumbar and sacral segments of the cord. The exact mechanism of the degeneration is not known and several theories have been advanced. Grossly there is shrinking of the posterior portion of the cord, which may appear pinkish or grayish in color. The pia-arachnoid of the cord is thickened and adherent. Microscopically there is degeneration of the nerve fibers of the posterior columns with

axones degenerate. Iritis, kerato-iritis, neuroretinitis, and iridocyclitis are characterized by an infiltrate of lymphocytes and plasma cells, increased vascularization, and fibrosis. Scarring of the cornea leads to opacities, and punctate scars may be noted in the retina.

BONES.—In the bones, gummas are not uncommon. They are similar to gummas elsewhere and are therefore osteolytic. The periosteum may be involved in a low-grade inflammatory process characterized by the typical infiltrate, fibrosis, and osteoplastic features. The painful periosteal node is a form of localized syphilitic periostitis; however, the periosteum may be diffusely involved and may be associated with an underlying osteitis which results in a thickening of the entire shaft. Osteomyelitis may occur with lymphocytic and plasma cell infiltrate, increased vascularization, and fibroblastic activity, with resulting osteoporosis in the early stages and osteoscleroses later when the new-formed connective tissue becomes converted into bone.

SKIN AND MUCOUS MEMBRANES.—Late syphilis of the skin, other than gumma, is characterized by a slight infiltrate of plasma cells, lymphocytes, and macrophages, increased fibrosis, and hyperkeratosis. These tertiary lesions may

therefore be tubercular, annular, psoriasisiform, and corymbiform. The hyperkeratotic lesions most commonly affect the plantar and solar surfaces. Loss of pigmentation may occur and patchy leukoderma results. Temporal and lateral alopecia is an occasional manifestation of tertiary syphilis. A papule, which may ulcerate, may develop at the site of the initial inoculation and is known as a monorecidive lesion. In syphilitic glossitis there is a patchy or diffuse interstitial infiltrate of lymphocytes and plasma cells and some fibrosis. Epidermization of the epithelium (leukoplakia) ensues and is considered precancerous. Minute multiple gummas may develop in the vocal cords.

OTHER VISCELAR MANIFESTATIONS.—Diffuse interstitial fibrosis with the characteristic infiltrate and vascular changes and parenchymal atrophy may affect the testis, pancreas, suprarenal, spleen, liver, heart, and rarely the lungs and stomach.

JUXTA-ARTICULAR NODES.—Small, painless, subcutaneous nodules, from a few millimeters to 4 cm. in diameter, sometimes develop about the joints, especially the elbows and knees. These are composed of whorls of fibrous connective tissue, infiltrated with lymphocytes, plasma cells, macrophages, and an occasional giant cell, with a tendency to perivascular distribution. Lipoid-laden foam cells may be present between the whorls. Central hyalinization frequently occurs. Spirochetes are not demonstrable.

Congenital Syphilis

Syphilis is transmitted by the infected mother to her offspring, usually during the first two years of the infection. After this period, the mother may bear healthy children. Syphilis rarely causes the termination of pregnancy in early months, and spirochetes are not found in the tissues of the fetus prior to the eighteenth week. It has been suggested that the well-developed Langhans' layer of the chorion forms a protective barrier against the spirochete. After sixteen weeks this is no longer a definite layer and infection in utero ensues. Syphilis is therefore a common cause of miscarriage. If treatment is started before the fourth month of pregnancy, 94 per cent of the offspring will be nonsyphilitic.

The course of congenital syphilis is similar to that of the secondary and tertiary stages of the acquired form. The first manifestations are caused from a spirochetemia which, when overwhelming, may result in death and expulsion of the fetus, or in neonatal death. If the fetus survives the spirochetemia, a certain degree of immunity develops, and lesions similar to those of the tertiary stage of the acquired form occur, but at

a more rapid pace. There is a higher degree of selectivity in the congenital luetic and the stigmata are characteristic. Hypersensitization and variations in immunity probably account for the variety of lesions, the rapidity of development and focalization.

Placenta.—In syphilitic stillbirths and in neonatal active syphilis, the placenta is enlarged and of a firmer consistency than usual. Microscopically there is slight lymphocytic and plasma cell infiltration and an increase in fibrous connective tissue. The walls of the small arteries are thickened by endothelial proliferation and intimal fibrosis. Spirochetes are usually demonstrable in stained sections.

Stillbirths and Neonatal Deaths.—If death has occurred a few days before expulsion, non-specific bullae and maceration will be noted in the skin. In overwhelming spirochetosis, spirochetes are demonstrable in all tissues and, other than evidences of delayed development, histologic changes may be absent. In neonatal deaths, lesions in the liver, lung, and epiphyses and cartilages are characteristic. The extensive lesions of the liver and lung are incompatible with life.

Grossly, the liver is enlarged and pale in color and of increased consistency. Microscopically, there is diffuse and active fibrosis which disrupts the architecture by snaring off groups and individual cells. There is the usual perivascular lymphocytic and plasma cell infiltration, and islands of myelopoiesis are large and numerous. Gummas of the liver may also occur and, in contradistinction to the late gummas, spirochetes are easily demonstrated.

The lungs appear pale and airless and are of a firm, fleshy consistency. Microscopically there is diffuse fibrosis, the epithelial cells of the alveoli are cuboidal, and the air sacs contain an infiltrate of lymphocytes and macrophages. This condition is known as pneumonia alba. Gummas may also occur in the lungs.

Diffuse fibrosis accompanied by lymphocytic and plasma cell infiltration may also be found in the pancreas, suprarenals, spleen, and heart. The pancreas and suprarenal cortex are frequently underdeveloped. The spleen, however, is usually enlarged and myelopoiesis is active. In the heart there may be focal fatty changes in the myocardium and edema. Foci of perivascular infiltration and fibroblastic activity may be present in the kidney and delayed development is evident by persistent nephrogenesis. The largest number of spirochetes are found in the liver and lungs, and next in order of frequency are kidneys, spleen, suprarenals, thymus, heart, cord, and aorta.

Osteochondritis is generally a constant finding in the syphilitic stillborn, and it may develop shortly after birth and is then a pathognomonic sign of infantile congenital syphilis. It is responsible for the stigma of saddle nose, seen so frequently in congenital syphilis, because of the destruction of the vomer. The epiphyseal cartilages are usually slightly enlarged and the epiphyses are easily detached. On section, the narrow gray epiphyseal line is

broadened and has serrated borders. The proximate portion of the metaphysis appears yellowish, and bluish islands of cartilage may be seen in the new-formed chondrogenic bone. Microscopically there is an increase in the fibrous tissue, lymphocytic and plasma cell infiltration. The new-formed bone is irregular and imperfect, and islands of cartilage are observed in the metaphysis. Spirochetes are found in abundance in films from the lesions.

The Stigmata of Congenital Syphilis.—In the living child, congenital syphilis may be divided into two groups, the infantile and tardive. Gummas may occur in both groups.

INFANTILE CONGENITAL SYPHILIS.—The period of infantile congenital syphilis extends from birth to the second year. Mucocutaneous and osseous lesions are the main features. Desquamative cutaneous eruptions occur on the palms, soles, buttocks, and periorally. Rhinitis (snuffles) is common. These changes are analogous to the secondary syphilitide of acquired syphilis, and the lesions are similar. Saddle deformity of the nose, because of destruction of the vomer, is a frequent manifestation, and epiphysitis may lead to separation of the epiphyses. Lesions in the liver and spleen produce hepatosplenomegaly, a generalized lymphadenopathy is frequently present, and neurosyphilis is not uncommon. The histopathology of the lesions of the bones, liver, and spleen are similar to those which occur in stillborn children. In 47 per cent the spinal fluid is positive. Neurosyphilis may result in retarded mental development, due to underdevelopment of the brain, and meningo-vascular syphilis may cause hydrocephalus. Choroiditis of the eye may occur in two forms, (1) circumscribed focal lesions which leave behind white scars and (2) peripheral fundic involvement leaving pigmented scars and a salt-and-pepper fundus. There is perivascular lymphocytic infiltration of the choroid, focal in the first and diffuse in the second. In the second form there is also hyperplasia of the pigment cells, which migrate into the retina and produce the spotted appearance.

TARDIVE CONGENITAL SYPHILIS.—Tardive syphilis develops after the second year. Rhagades may be present in the tardive phase as well as in the infantile. The eyes, the bones, and the teeth are the most frequently involved tissues. Interstitial keratitis with lymphocytic infiltration, vascularization, and scarring is the most frequent ocular manifestation. It is usually bilateral and frequently results in blindness. It may be accompanied by iridocyclitis.

Periostitis is common, especially of the tibia, and may be focal or diffuse. The periosteum is thickened and infiltrated with lymphocytes, and an excess of imperfect bone is formed. The tibiae are frequently bowed anteriorly (saber shins). Involvement of the periosteum of the cranial bones causes a deformity of the skull characterized by a square skull because of the prominent parietal and frontal bosses. Gummas may also occur in the bones, especially in the nasal bones, and a saddle nose may also be a stigma of this stage. Enlargement of the sternal extremity of the clavicle is usually a sign of congenital syphilis and occurs mostly on the right side in right-handed individuals. This is a late lesion and is due to hyperostosis from a syphilitic osteitis.

In the tardive phase 27 per cent of the congenital syphilitics have a positive reaction on the spinal fluid and 20 per cent of the untreated cases develop neurosyphilis. Syphilitic meningitis and meningo-vascular syphilis may develop at an earlier stage than paresis and tabes. Eighth nerve deafness and optic atrophy may also occur. Aortitis occasionally develops in congenital syphilis and aneurysms have been reported.

HUTCHINSON'S TEETH.—In 1858 Hutchinson described the appearance of the permanent teeth of children which is a stigma of congenital syphilis. At the time of spirochetal dissemination in the fetus, the development of the enamel of the permanent teeth is impaired and these teeth erupt with hypoplastic crowns. The incisor teeth are screw-driver-shaped or peg-shaped. There is convergence of the lateral borders of the incisors and first molars, and a midincisal notch develops due to the lack of the dentino-enamel junction. (See discussion also on page 740.)

YAWS

The treponematoses yaws (framboesia, pian, bubas), in its clinical course, pathology, and response to therapy, bears a striking resemblance to syphilis. The three stages—primary, secondary, and tertiary—are not as distinctive; one stage may pass gradually into the other and the patient may never be free from some manifestations over a period of years. Yaws is transmitted by intimate contact and probably by flies of the genus *Hippelates*, and it is usually acquired in childhood before the age of 15 years. Sexual transmission is possible though exceptional, and it is rarely, if ever, congenital. The pathologic processes affect chiefly the skin and bones; however, lesions similar to syphilis have been observed in the aorta, heart, adrenals, liver, pancreas, brain, meninges, and testes.

Cause

The causative organism, *Treponema pertenue*, was discovered by Castellani in 1905 and cultivated by Noguchi in 1912. The spirochete is morphologically indistinguishable from the spirochete of syphilis; however, the lesion produced by inoculation of rabbits and monkeys differs from that of syphilis. Cross immunity develops between syphilis and yaws, but the immunity is not as great as that afforded to each other, and in yaws the immunity takes a longer time to develop.

Distribution

Yaws occurs chiefly in damp tropical climates, in regions of low altitude, and where unsanitary conditions prevail. It is common, therefore, in the islands of the Pacific, Southeastern Asia, West Indies, and some tropical areas of South and Central America. A few imported cases have been reported in continental United States.

The Primary Lesion

The initial lesion, the mother yaw, usually single, arises at the site of inoculation on an

exposed portion of the body, especially on those parts subjected to trauma, and therefore is most commonly found on the lower extremities. After an incubation period of ten days to several weeks, the primary lesion begins as a small papule and enlarges rapidly, either by spread of the single papule or by coalescence of several, and attains a size of from 2 to several centimeters. It appears as an encrusted, cauliflower elevation. When the crust is removed, the surface presents corrugations and morulations and the lesion appears red and pulpy like a raspberry (framboesia). It may heal spontaneously, sometimes leaving a thin depigmented scar surrounded by a hyperpigmented halo, or, rarely, it may leave no trace. Often, however, the hypertrophic papule may persist and become a part of the secondary stage and may even remain as a chronic ulcer in

The Secondary Lesions

Secondary skin eruptions occur two weeks to three or more months after the primary, and result from dissemination of the organisms by the blood and possibly also from auto-inoculation. They are usually limited to the skin and rarely involve the mucous membranes. The circumoral and anogenital regions are sites of predilection. They are first observed as scaly macules, which are followed in a few days or weeks by groups of folliculopapules, small isolated papules, or typical framboesiform lesions 1 to 2 cm. in diameter. The small papules may sometimes coalesce in a circular pattern and produce "ring worm" yaws. The eruption may last from a few weeks to two years and may disappear without a trace; how-



Fig. 185.—Yaws, primary lesion (mother yaw or chancre). (Courtesy Dr. Herbert S. Alden, Atlanta, Georgia, and Dr. P. D. Gutierrez, University of the Philippines, Manila.)

the tertiary phase. Spirochetes have been found in the regional lymph nodes, which may or may not be enlarged.

Histopathology of the Primary Lesion.—The elevated papillary lesion is produced by hypertrophy and elongation of the rete pegs and enlargement of the papillae. The superficial part of the epidermis is thickened by a moderate amount of keratinization. Foci of edema, hydropic degeneration, and necrosis, which are infiltrated with polymorphonuclear leukocytes, are present in the deeper epidermis, and the amount of melanin is reduced. Edema and polymorphonuclear leukocytic infiltration are observed in the papillae, especially in proximity to similar areas in the epidermis. The dermis is infiltrated with a distinct zone of numerous plasma cells, fewer lymphocytes, and an occasional eosinophilic leukocyte which are especially abundant about the tubular structures. The lymphatics and capillaries are dilated and the endothelial cells swollen. Spirochetes are found in abundance in the epidermal and dermal foci of edema, necrosis, and leukocytic infiltration, but are few in number in the deeper corium.



Fig. 186.—Yaws, secondary framboesiform lesions. (AFIP No. 39201.)

ever, intervals of latency may be punctuated by recurrences over a period of five to ten years. Occasionally, a few lesions may ulcerate and follow a destructive course.

Histopathology of the Secondary Lesions.—The secondary lesions resemble the mother yaw.

reduced centrally and at the margins may be increased. A few macrophages may be seen in the infiltrate of the dermis and slight fibroblastic proliferation occurs. While the plasma cells remain as the most abundant cell of the exudate, numerous polymorphonuclear leuko-



Fig. 187.—Crab yaws. (Courtesy Dr. Herbert S. Alden, Atlanta, Georgia, and Dr. P. D. Gutierrez, University of the Philippines, Manila.)



Fig. 188.—Frambesiform lesion of yaws. Note the enlarged papillae and the elongation of the rete pegs. Several foci of edema and polymorphonuclear leukocytic infiltration can be seen in the lower epidermis and contiguous papillae. It is in these sites that numerous spirochetes are demonstrable by silver impregnation. (AFIP No. 92617.)

The hypertrophy of the rete pegs is slight in the early macules and papules but increases as the frambesiform lesions evolve. Keratinization is more pronounced and the surface becomes covered with a crust of dried serum, wandering cells, and bacteria. The pigment is

cytes accumulate in the edematous elongated papillae, invade the epidermis, and small abscesses are formed. As in the primary lesion, the spirochetes are numerous in the intraepithelial foci and the subjacent papillae, and fewer in number in the deeper corium.

Crab Yaws

Keratosis plantaris and palmaris occur directly after the secondaries or as long as twenty years later. Because of the peculiar gait of those affected with the painful plantar lesions, it is called crab yaws. Hyperkeratotic plantar lesions are common, generally progressive, and, without treatment, may persist for the remainder of life. There may be generalized hyperkeratosis, with painful fissures or isolated cornlike hyperkeratosis, embedded in the horny layer. This clavus is painful, easily detached, and falls off spontaneously. Gradually, the lesions may extend to the sides and back of feet and hands. The histopathology is similar to that of the secondaries and in addition there is pronounced hyperplasia and hyperkeratinization of the epithelium. The clavus is composed of laminated horn cells which are separated from the rest of the epithelium and when detached leave small pits. A few foci of macrophages and giant cells may be found in the dermis. Spirochetes are usually not demonstrable.

Tertiary Lesions

The late destructive manifestations are indistinguishable from syphilis. Skin and bones are most commonly involved. The lesions may follow soon after or accompany the secondaries and often produce severe mutilation.

Skin.—Chronic ulcers are frequent and sometimes arise from earlier lesions. More often they appear after an interval of months or years, arising from broken-down gummatous nodules of the dermis and subcutaneous tissue which have a predilection for the extremities. The ulcers may heal after destruction of much tissue and lead to contractures and deformities. The histology is similar to the secondaries, but deep in the dermis macrophagic tubercles and giant cells may be observed.

Gangosa.—Ulcerating gummatous lesions may start in the soft palate, nose, or pharynx, enlarge rapidly, and destroy much of the nose and palate, leaving the upper lip as a bridge across a gaping cavity. This shocking mutilation is known as rhinopharyngitis mutilans, or gangosa, meaning nasal voice.

Bone.—Osteoperiostitis, especially of long bones, is a frequent tertiary manifestation. Localized gummatous nodes on the tibia, radius, and ulna may extend to the skin from the periosteum, and destructive ulceration results. The diffuse form most commonly involves the tibia of children and produces saber shins because of anterior bowing and the thickened shaft. Goundou is a peculiar exostosis of the nasal processes of the superior maxillae, which project downward and outward and may interfere with vision. This lesion is considered a sequela of yaws.

Juxta-articular Nodes.—Months or years after the secondaries, painless, smooth, hard, subcutaneous nodules may occur in the neighborhood of the larger joints, especially elbows and knees, often after all other evidence of active yaws has disappeared. They are composed of layers of dense connective tissue which enclose a central necrotic mass. There is peri-

vascular lymphocytic and plasma cell infiltration, and collections of macrophages laden with lipoids are observed. The juxta-articular nodes yield slowly to treatment.

Visceral Lesions.—Involvement of the central nervous system and cardiovascular system is infrequent. Visceral gummas are extremely rare.

In general, it may be said that the histologic criteria for differentiating lesions of yaws and syphilis are unreliable. However, it should be noted that epidermal lesions are more prominent in yaws as contrasted to dermal involvement in syphilis, and endarteritis is not outstanding.

BEJEL

A nonvenereal treponematosis, thought to be syphilis, occurs in pandemic form in the Bedouins of the valley of the Euphrates River and especially in the nomadic Bedouins of the deserts of Syria and Iraq. It is acquired in childhood and affects 60 per cent of the preadolescent population. This form of syphilis is known as bejel by the Arabs, and infection carries no stigma. The course of the disease is different from the usual type of syphilis because of childhood inoculation and the possible influence of race, climate, nutrition, trauma, and irritation.

The primary lesion is rarely observed and probably occurs in the mouth. The first manifestation is the presence of mucous patches on the oral mucosa, although a variety of skin lesions and ulcerations may occur. The lesions resemble, clinically and pathologically, the secondaries of syphilis but may be complicated by superimposed infections. Lymphadenopathy is common. The first manifestations usually disappear spontaneously within a year, and the disease may remain quiescent for a period of years.

The late stage is characterized by involvement of bones, skin, and the mucous membranes of the nasopharynx. The most frequently observed lesions are gummatous ulcerations of the mucous membranes; periosteal and endosteal proliferation with varying degrees of rarefaction of the shafts of the long bones, especially tibia and ulna; hyperkeratoses of plantar surfaces of feet with a tendency to fissuring; and patchy areas of depigmentation on the hands and feet. Juxta-articular nodes have been reported. The absence of serious damage to the nervous system and viscera is characteristic. Because infection occurs in early childhood and the disease is usually in the late stage at the time of marriage, congenital infection is rare. The Wassermann reaction is positive and the lesions respond to antisyphilitic therapy.

PINTA

Pinta (*mal del pinto, carate, tiña*) is a nonvenereal chronic endemic treponematosis which is characterized by three stages of cutaneous manifestations. It is not congenital. The name pinta, meaning painted, is descriptively appropriate because of the variegated color display of the cutaneous lesions. The Conquistadores apparently observed pinta and wrote about it,

but the first classic description was written by Leon in 1860. Pinta, like the other treponematoses, responds to arsenical therapy.

Distribution

Pinta is largely confined to the American tropics and is limited almost exclusively to the dark races. It is prevalent in Mexico, Colombia, and Venezuela and is found to a less extent in Peru, Ecuador, Bolivia, Brazil, Central America, and the islands of the West Indies. Cases resembling pinta have been reported in northern Africa, the Philippines, India, Iraq, and the islands of the South Pacific, and a few cases have been observed in continental United States.

Males and females are equally affected. The disease is rare in infancy and is usually acquired between the tenth and twenty-fifth year of age. It occurs chiefly among the poorer classes in rural and suburban districts, and especially in those living in unsanitary surroundings and lacking in personal hygiene.

Cause

Pinta was considered a cutaneous mycosis for years. Menk, however, in 1926, found that a positive Wassermann reaction was obtained in patients with pinta, and the following year Herrejon suggested the possibility of a spirochete as the causative organism. This prediction was fulfilled when, in 1938, Grau Triana and Armenteros recovered a spirochete in the lymph of the cutaneous lesions and affected lymph nodes. This observation was confirmed by Leon y Blanco and Pardo-Castello and they also demonstrated spirochetes in sections of tissue. Leon y Blanco reproduced the disease by inoculating himself and other volunteers with serum from lesions, and he identified the treponema as a distinctive organism by successful inoculation and reproduction of the disease in latent syphilites. He, furthermore, reported two patients with pinta who acquired syphilis. The organisms have been cultivated in nervous tissues of mouse embryos.

The treponema is morphologically indistinguishable from that of yaws and syphilis. It commonly varies in length from 12 to 18 microns and spirals occur at intervals of 1 micron. Different observers have ascribed different names to the spirochete; the most frequently used are *T. carateum*, *T. pintae*, and *T. herrejoni*.

The exact method of transmission of pinta is undetermined, but probably it is by prolonged and intimate contact. Flies (*Hippelates*) and bedbugs (*Cimex lectularis*) have been suggested as possible vectors.

Immunity to reinfection is delayed. The incidence of positive Wassermann and related reactions increases with the duration of the disease. Serologic tests may be negative while the primary remains alone, but the percentage of positive tests increases from 60 in the secondary stage to nearly 100 in the later dyschromic stage.

Clinical Course

Primary Stage.—The exposed parts of the body are the usual sites of the primary lesion, which begins as a papule at the site of inoculation after an incubation period of seven to

twenty days. Within thirty to fifty days the papule spreads peripherally and becomes an erythematous squamous patch 4 or 5 inches in diameter. Satellite papules may appear, from which coalescing erythematous squamous patches develop. The appearance of the lesions varies in different patients and also in the same individual. Trichophytic, psoriasisiform, and lichenoid lesions are the types most frequently observed. Ulceration never occurs.

Secondary Stage.—Within five to twelve months, disseminated macules and papules appear. These are known as pintids or empeines. The macules and papules rapidly change into diversely outlined erythematous squamous plaques. The evolving initial lesion becomes indistinguishable from the secondaries. Large portions of the body may be symmetrically involved; however, the skin of the extremities and the skin overlying bony prominences are sites of predilection. The patches, at first pink, soon darken, and the color will vary from brown to slate blue or black according to the degree of the natural pigmentation of the individual. Subjective symptoms, other than itching, are absent. The lymph nodes may enlarge slightly. Eosinophilia is common.

Tertiary or Dyschromic Stage.—In the course of several months dyschromic lesions develop. Areas of erythema and hyperpigmentation occur chiefly on the extremities and face, over bony prominences, and at the waistline. Centrally the lesions undergo involution and become achromatic, while the darker border slowly advances peripherally and in the course of several months, the individual lesions attain a size of 1 or 2 inches. The color of the tertiary, like the secondaries, depends on the natural pigmentation of the individual and also on the stage of evolution. Fine branny scales frequently cover the lesions. After several years, vitiligo patches evolve as central depigmentation proceeds, and finally the skin becomes atrophic.

Follicular keratoses, especially of the palms and soles, may develop in the tertiary stage, and thickening and pigmentation of the nails are occasionally observed. The mucous membranes are rarely affected, but infrequently blue patches occur on the lips and oral mucosa.

Hypertension, juxta-articular nodules, and cardiovascular lesions are rare late manifestations. Aortitis, aneurysms, and disturbances in the heart sounds have been noted. Increased globulin content and a positive Wassermann reaction of the spinal fluid are found in 10 per cent of the cases.

Histopathology

Primary and Secondary Lesions.—The epidermis is thickened and the rete pegs elongated. The stratum corneum is thin and flaky. There is intercellular edema of the stratum germinativum and the epidermis is infiltrated with a few leukocytes. In the early lesions there is an increase in the pigment of the basal cells, but with chronicity the intraepithelial pigment diminishes. Numerous melanophores accumulate in the papillary layer of the corium and progressively increase in number as epidermal pigment decreases. The corium is edematous and in-

filtrated with plasma cells, lymphocytes, and a few histiocytes, and an occasional neutrophilic and eosinophilic leukocyte. The infiltrate extends along the tubular structures. The endothelium of the blood vessels is invaded and sometimes dissociated by inflammatory cells. With silver impregnation the spirochetes are readily demonstrated in the epidermis and hair follicles and occasionally in the dermis.

Tertiary Cutaneous Lesions.—In the tertiary lesions the number of melanophores varies according to the degree of depigmentation of the lesion, the infiltrate gradually diminishes, the epidermis atrophies, and the papillae disappear as the corium undergoes fibrosis. In the hyperkeratotic lesions a thick layer of keratin accumulates on the surface. Spirochetes are sparsely distributed in the epidermis.

Lymph Nodes.—The distinguishing feature of the chronic lymphadenitis, which terminates in fibrosis, is the presence of pigment, hyaline corpuscles, and eosinophiles.

the cause of swineherd's disease; and *Lept. canicola*, the cause of canicola fever, produce similar but milder symptoms than *Lept. icterohaemorrhagiae*, the agent of Weil's disease or spirochetal jaundice. Additional strains are *Lept. bataviae* and *sejroe*. Canicola fever and Weil's disease are world-wide in distribution.

With the exception of *Lept. canicola* and *Lept. pomona*, rodents are the common reservoirs of infection and 10 per cent of wild rats are infected. The infection is transmitted by the urine and feces of rodents harboring the organisms. Canicola infection is transmitted from dog to dog and dog to man in a like manner, and 7 per cent of leptospiral diseases in the

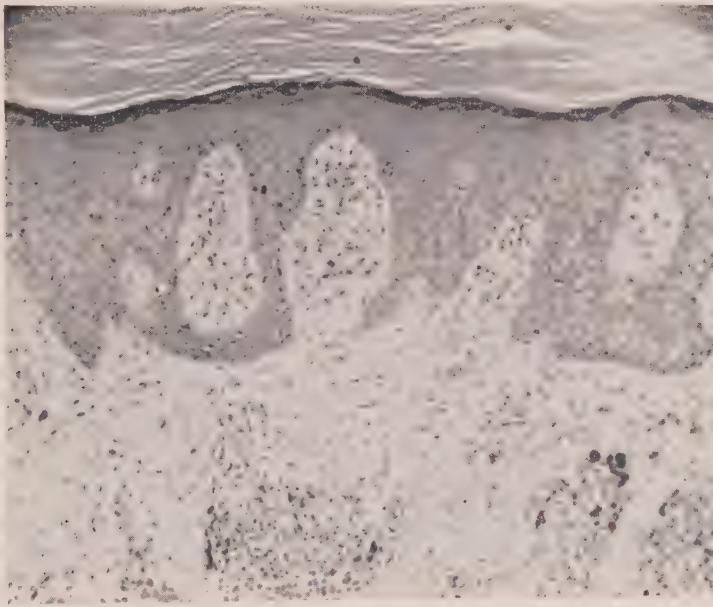


Fig. 189.—Pinta. Histology of hyperkeratotic lesion. (AFIP No. 99736.)

LEPTOSPIROSES

The leptospiroses include a group of diseases which are caused by related organisms and which exhibit similar manifestations. The causative organisms are morphologically alike but differ in their antigenic properties and in their virulence for man and animals. *Leptospira grippotyphosa*, the cause of swamp fever in southeastern Europe; *Lept. hebdomadis*, the cause of seven-day fever in Japan and India; *Lept. autumnalis*, the cause of autumnal fever in Japan; *Lept. pomona*,

United States are caused by *Lept. canicola*. Pomona infection is transmitted from hog and cattle to man.

Weil's Disease

Weil's disease (spirochetal jaundice) was described by Weil in 1886. In this country there is an apparent increase in the number of cases and many mild cases are probably overlooked.

Cause.—The causative organism was discovered by Inado and Ido, in 1915, and classified by Noguchi, in 1918, as *Leptospira icterohaemorrhagiae*. The organism is 6 to 15 microns long and 0.2 to 0.5 micron wide, and the fine, tightly

wound spirals enclose an axial filament. It is rapidly motile. The organisms have been successfully cultivated.

Wild rats are the chief reservoir of infection, but organisms have been demonstrated in field mice, foxes, cats, pigs, horses, dogs and gophers. Rat to rat infection results from contamination of food by excreta and less commonly by intercourse. Transmission to man occurs most frequently from contact with the excreta of infected rats and rarely from bites. The organisms may penetrate the unbroken skin, nasal or conjunctival mucosa, or may gain entrance through the gastrointestinal tract, usually through the medium of polluted water. Leptospiras are able to survive in neutral or slightly alkaline stagnant water for three or more weeks. Weil's disease is an industrial hazard and occurs frequently in sewer workers, fish handlers, miners, rice-field workers, slaughterhouse employees, sugar-cane cutters, and farmers. Bathers in polluted water may become infected.

Clinical Course.—The incubation period varies from 2 to 21 days. The clinical course is conveniently divided into three stages: septicemic, toxic, and convalescent. The intensity of the disease varies and many patients without jaundice pass directly from the first stage to the period of convalescence.

Pathologic Changes.—Generalized jaundice is invariably observed in fatal cases. Hemorrhages in the heart, liver, kidneys, and voluntary muscles contribute to the morbid anatomy of these organs and also occur in nasal and gastrointestinal mucosa, skin lungs, adrenals, pancreas, pleura, peritoneum, spleen, eye, bladder, brain, and meninges.

LIVER.—Grossly the liver is enlarged, firm, and of a deep yellow color. The periportal connective tissue is infiltrated with lymphocytes and neutrophilic leukocytes. Perisinusoidal edema, parenchymatous degeneration, and dissociation of the hepatic cells are characteristic. Slight to extensive necrosis may occur, usually in the center of the lobules. Mitotic figures are frequently observed in the hepatic cells. Bile stasis is striking and hemorrhages are common. Spirochetes are demonstrable by silver impregnation in the interstitial tissue, hepatic cells, and Kupffer cells.

KIDNEYS.—The kidneys are grossly enlarged, firm, and edematous. Cloudy swelling and fatty degeneration of the tubular epithelium may proceed to necrosis. The tubules contain casts, detritus, and bile-laden macrophages. There is hyperplasia and swelling of the glomerular epithelium, and the local toxic effect of the leptospiras on the capillary endothelium may cause glomerular hemorrhage as well as interstitial and pelvic petechiae. An interstitial infiltrate of lymphocytes and neutrophilic leukocytes may be evident between the glomeruli. Leptospiras are found in large numbers in the tubular epithelium and interstitial tissue.

SKELETAL MUSCLE.—In early lesions, focal, small and medium-sized vacuoles occur within the fibers. At both ends and along the margins of the focus of degeneration the sarcoplasmic cells proliferate and form syncytial masses. These invade the degenerated segment and form large multinucleated cells. Few neutrophilic

leukocytes infiltrate the necrotic area. When new formation of fibrils begins, repair is rapid. In the more severe lesions necrosis is extensive, the fibers are disrupted, and lymphocytes and plasma cells infiltrate the interstitial tissue around the focus. Fibroblasts repair the damage. The presence of argyrophilic fragments is suggestive of leptospiras. These changes are sufficiently characteristic for diagnostic purposes and the gastrocnemius muscle is the site of election for biopsy.

HEART.—Degenerative changes similar to those in the skeletal muscle occur, and petechiae may be observed in the myocardium, endocardium, and pericardium. Fibrinous pericarditis results from uremia, and vegetative endocarditis has been reported.

OTHER CHANGES.—In the central nervous system there may be perivascular infiltration of lymphocytes and the neurones may exhibit chromatolysis and neuronophagia. The leptomeninges may be infiltrated with lymphocytes and plasma cells. The spleen rarely is enlarged from reticuloendothelial hyperplasia, and free macrophages laden with fragments of erythrocytes may be present in the pulp. Central necrosis has been observed in the pancreas. Aseptic meningitis and iridocyclitis are common manifestations of infection with *Lept. canicola* and *pomona*.

Relapsing Fever

Relapsing fever is an acute spirochetal infectious disease which is characterized by recurrent paroxysms of fever and an associated toxemia and periodic spirochetemia. The infection is transmitted by two agents, lice (*Pediculus humanus*) and ticks (genus *Ornithodoros*).

Cause.—The causative organism of the louse-borne infection was discovered in 1868 by Obermeier. The spirochetes of relapsing fever are morphologically indistinguishable from one another, they possess marked physical and antigenic instability, and reliable techniques for cultivation have not been developed; therefore, classification of the various strains is unsatisfactory. All strains are considered as probable variants of *Borrelia recurrentis*.

The spirochete is 10 to 45 microns long, averaging 22 microns, and 0.3 micron thick, and contains three to six loosely wound spirals.

Louse-Borne Infection.—In the louse-borne disease, man-to-man infection is transmitted by lice (*Pediculus humanus*), and where lice prevail, epidemics may occur, sometimes concomitantly with typhus. The bites of the lice are innocuous and the organisms are not present in their feces. Inoculation results from the crushing of the lice, so that the liberated spirochetes penetrate the skin through the abrasions which were inflicted by scratching. It is possible that infection may also occur by transference of the organisms to the conjunctival sac.

Tick-Borne Infection.—Rodents are the usual reservoir of infection of the tick-borne disease although other animals may serve as intermediary hosts. Organisms have been demonstrated in monkeys, opossums, dogs, armadillos, cattle, horses, mules, badgers, and foxes. The spirochetes are transmitted through the bite or from the coxal fluid of ticks of the genus

Ornithodoros. Endemic foci persist because of the transovarian route of transmission in ticks, and epidemics may sometimes occur.

Distribution.—Louse-borne relapsing fever is prevalent in Eastern Europe and Asia, and the chief focus of the tick-borne disease is Central and South Africa. Endemic centers for the latter, however, exist in many parts of the world, and sporadic cases occur in the United States.

Clinical Course.—After an incubation period from 3 to 16 days, a short febrile period of 4 to 10 days begins and ends abruptly. Similar but often milder and shorter paroxysms follow at intervals of 3 to 12 days. Occasionally the disease subsides spontaneously after two or three relapses in the louse-borne infection, but as many as ten may occur in African tick fever. The febrile episodes are usually accompanied by toxic symptoms: severe headaches, dizziness, muscular pains, nausea and vomiting, and prostration.

Spirochetes are frequently demonstrable during the febrile periods in thick films of blood and are regularly recovered by inoculation of the blood of the patient into white mice and rats. Spirochetes have been found in the cerebrospinal fluid, sputum, urine, skin lesions, and prostatic fluid of patients.

The Wassermann reaction is positive in 20 per cent of cases, and a specific complement fixation test has been developed.

The fatality rate varies in different localities and in various epidemics from 0 to 50 per cent.

Pathologic Changes.—The spleen, liver, kidneys, heart, capillaries, brain, and meninges are frequent sites of pathologic alterations.

The spleen is usually enlarged and soft, often weighing 300 to 400 grams. Small infarcts are seen, and numerous yellowish foci of necrosis occur, especially in the neighborhood of the hyperplastic lymph nodules. The foci are infiltrated with large macrophages, scattered plasma cells, and a few polymorphonuclear leukocytes. With silver impregnation numerous spirochetes are demonstrable in the peripheral zone of the necrotic foci. The sinuses are congested and contain macrophages laden with hemosiderin. Hemorrhages occur in the pulp.

The liver is often enlarged, and intense congestion accentuates the vascular markings. The hepatic cells in the mid and central zones of the lobules may undergo fatty degeneration. Bile stasis and imbibition are noted in the parenchyma. The Kupffer cells are prominent and contain argyrophilic debris, probably phagocytized degenerated spirochetes. Well-preserved spirochetes may also be found.

In the kidneys there is cloudy swelling and fatty degeneration of the convoluted tubular epithelium. Hemorrhage into the glomerular tufts is not uncommon. Cloudy swelling and fatty degeneration of the myocardial fibers occur, and vegetative endocarditis has been reported. Capillary hemorrhages result from endothelial injury and are found in many parts of the body: pleura, peritoneum, lungs, skin, nasal, oral and gastrointestinal mucosa, glomerular tufts, meninges, and brain. Meningeal and cerebral congestion is common, and spirochetes are occasionally found in sections from the brain. Or-

ganisms have also been found in the bone marrow. In fatal cases the presence of jaundice is almost constant.

Sodoku (Rat-Bite Fever)

Sodoku (*so*—rat, *doku*—poisoning) is a paroxysmal febrile disease which is caused by *Spirillum minus*. The portal of entry of the infection is usually through the bite of a wild rat; however, other animals which harbor the spirilla may transmit the disease in a similar manner. Cases have been reported from the bite of dogs, cats, pigs, squirrels, ferrets, and weasels. The relapsing course of the disease is characterized by cyclic reactivation of the initial lesion with invasion of the blood stream by the spirilla.

Distribution.—Because the chief reservoir of infection is the wild rat, the disease is worldwide in distribution. The local incidence will naturally vary according to man's proximity to the wild rat and to the epizootic level of infection. In the United States the percentage of rat infection is low.

Cause.—Futaki, Takaki, Taniguchi, and Osumi discovered the spirillum in 1916 and named it *Spirochaeta morsus muris*. In 1924 Robertson classified the organism as a spirillum and renamed it *Spirillum minus carteri*, because Carter had given a similar name to an organism which he had discovered in an Indian wild rat in 1887. *Spirillum minus* usually appears as an actively motile short organism, 1.7 to 5 microns long, with 2 to 6 spirals, and one or more flagella originate from each extremity. Only recently has the organism been cultivated.

The infection is transmitted, as a rule, by the bite of a wild rat. The spirilla enter the wound probably from secretions of the lacrimal glands, upper respiratory tract, or lungs, and possibly from the blood of the rat through a gingival abrasion. The organisms are disseminated by the blood from the initial lesion.

Clinical Course.—The wound inflicted by the bite of the animal apparently heals within a few days unless there is secondary infection. After a variable incubation period, which averages two weeks, there is an abrupt onset of fever, with or without a chill, and accompanied by anorexia, headache, malaise, nausea and vomiting, and joint and muscle pains. In severe infections there may be cloudiness of the sensorium, stupor, or delirium. The initial lesion is reactivated and becomes inflamed and indurated. Ulceration may ensue and impart a chancrelike quality to the lesion. There is an associated lymphangitis and regional lymphadenitis. The febrile episode subsides suddenly in three to seven days, and successive paroxysms continue at intervals of two to fourteen days. There is usually simultaneous periodic activation and regression of the inflammation of the local lesion. Gradually the relapses diminish in intensity and occur at longer intervals, and the disease may subside spontaneously after a period of weeks, months, or, rarely, years.

A maculopapular, erythematous rash, sometimes of a dark, purplish hue, and beginning near the primary lesion, appears at varying intervals, the intensity increasing and decreasing

with the paroxysms. There may be generalized enlargement of the lymph nodes, and the liver may be palpable. The Wassermann reaction on the blood is positive in 50 per cent of cases. The spirillum has been demonstrated in tissue fluid expressed from the wound, by aspiration of a lymph node and from the cutaneous eruption. On rare occasions, darkfield examination of the blood may reveal the organisms, but the diagnosis is usually established by recovery of the spirilla by inoculation of the patient's blood into mice, rats, and guinea pigs. The mortality rate is low.

Pathologic Anatomy.—The indurated chancre is hyperemic and edematous; there is dense round-cell infiltration of the corium and necrosis of the overlying epithelium. The regional lymph nodes as well as other nodes are hyperplastic.

Toxic parenchymatous changes are noted in the viscera: cloudy swelling, fatty degeneration, and central necrobiosis with hemorrhage of the liver; cloudy swelling, fatty degeneration, necrobiosis, and desquamation of the tubular epithelium of the kidney; cloudy swelling of the myocardial fibers; hyperemia and hyperplasia of the spleen; hyperemia and edema of the meninges; and degenerative changes of the neurones of the brain and cord. The spirilla have been found in casts of the lower convoluted tubules and of Henle's loops of the kidney; in the cortical cells of the suprarenal; in the interstitial tissue of the testes; and in the regional lymph nodes.

Vegetative endocarditis superimposed on a rheumatic valvular lesion has been reported.

Rat-Bite Fever and Haverhill Fever

Rat-bite fever caused by *Streptobacillus moniliformis* should not be confused with sodoku. However, it is of equal importance as judged by the number of cases reported. Streptobacillary infection may be acquired in two ways, by the bite of a rodent and by the ingestion of food or water which has been contaminated with the excreta of rodents which harbor the organism. There are, therefore, two nominal entities: (1) rat-bite fever and (2) Haverhill fever, which are caused by the same organism and which differ only in the manner of inoculation.

Cause.—Schottmüller, in 1914, discovered the causative agent of rat-bite fever and named the organism *Streptothrix muris-ratti*. In 1925 Levaditi, Nicolau, and Poincloux found that a similar organism (*Streptobacillus moniliformis*) was the etiological agent of certain forms of infectious polymorphous erythema accompanied by polyarthritis. Place, Sutton, and Willner, in 1926, reported an epidemic of arthritic erythema which was thought to be milk-borne. Parker and Hudson isolated the causative organism of this epidemic and named it *Haverhillia multiformis* because the epidemic occurred in Haverhill, Massachusetts. The food-borne disease is therefore commonly referred to as Haverhill fever. It is now agreed that the causative organisms of rat-bite fever and Haverhill fever are identical and *Streptobacillus moniliformis* is the preferred name.

The organism is nonmotile, gram-negative, slender, and curved, 2 to 15 microns long, grows in chains and sometimes branches. Ball-shaped swellings appear in the filaments. They have been recovered from rats with bronchopneumonia and from white mice with a disease characterized by septicemia, polyarthritis, and myocarditis.

Clinical Course.—The incubation period of streptobacillary rat-bite fever is less than ten days. There is usually prompt healing of the wound without induration and, in contradistinction to the behavior of the lesion of sodoku, there is no subsequent reactivation nor uncomplicated lymphadenitis. Rat-bite fever and Haverhill fever have a similar clinical course. The onset is abrupt, with chills, fever, vomiting, intense headache, malaise, and prostration. Symptom-free remissions and febrile episodes of irregular duration and intervals usually occur over a period which may vary from two weeks to months. The fever is usually accompanied by a rubellaform, morbilliform, or petechial cutaneous eruption. Arthritis of a varying degree is a frequent manifestation and is characterized by painful swelling of several joints and the presence of excess fluid. The leukocytes are moderately elevated. The complications are pneumonia and endocarditis. The mortality rate is 10 per cent. The organism may be recovered by culture or animal inoculation, from the blood, from the joint fluid, and from the cutaneous eruption.

Pathologic Anatomy.—In fatal infections with *Streptobacillus moniliformis*, very few necropsies have been reported and the findings are those of a septicemia.

Cloudy swelling of the liver and kidneys and an excess amount of fat in the hepatic cells are generally observed. Bronchopneumonia and ulcerative endocarditis are probable evidences of localization of organisms. As a result of the endocarditis, infarcts may result, especially in the spleen and kidneys. The spleen is moderately enlarged and hyperplastic. Subacute interstitial myocarditis, hepatitis, and nephritis have been reported, which are characterized by focal infiltration of lymphocytes, plasma cells, a few neutrophilic leukocytes, and an occasional foreign body giant cell. Degeneration of the parenchyma ensues, which is associated with fibroblastic proliferation. In the liver the interlobular connective tissue may be increased. In one reported necropsy, structures resembling the organism were observed within the neurones of the ganglia which are situated near the suprarenal and in the circulating polymorphonuclear leukocytes of the blood.

FUSOSPIROCHETOSIS

Ulcerative lesions of the mouth, pharynx, and genitals and excavation and gangrene of the lungs may result from infection with the fusospirochetes of Vincent (Plaut-Vincent or Miller-Plaut-Vincent). In most instances the fusospirochetes are secondary invaders; however, they may alter the pathologic picture to

such an extent as to obscure the primary disease. In fewer instances they are primary bacterial invaders, but even then there are commonly predisposing factors. Fusospirochetes rarely affect healthy tissue; thus the organisms may be considered as saprophytic opportunists. Infections have been produced in animals usually after trauma or after inoculation with other pathogens.

Organisms

The fusospirochetes were described first by Miller in 1890 and then by Plaut in 1894. Three forms of organisms are encountered: the fusiform bacillus, a spirochete, and a vibrio. The bacilli appear as straight or curved rods with rounded or pointed ends and are 0.8 to 1 micron wide and 3 to 10 microns long. The spirochetes are 4 to 15 microns long and possess 2 to 20 coils. The vibrios are 2 to 5 microns long and 1 micron thick with a number of flagella. Most observers believe that the different organisms act symbiotically; however, a few claim that they are transitional forms of a single organism. The spirochetes are the most prevalent organism found in the severe lesions. The organisms are sometimes demonstrable in the mouth and in the smegma of the vulva or penis of normal individuals. They are frequently encountered in the surface debris of various oral and genital lesions and also in bronchiectatic cavities.

Fusospirochetal Diseases

Ulceromembranous Gingivitis and Stomatitis, or Trench Mouth.—The predisposing causes of this affection are lack of oral hygiene, scurvy, mercurial or bismuth stomatitis, and, in children, herpes simplex. The gingival margins are first involved and the lesion may extend to contiguous surfaces of the mouth. The gums appear swollen, spongy, and hyperemic, and bleed readily to touch. Yellowish-gray sloughs may form. The gums are tender and the breath fetid.

Vincent's Angina.—Painful membranous ulceration of the throat, when caused by the fusospirochetes, is known as Vincent's angina because Vincent in 1896 described certain types of ulcerative tonsillitis caused by these organisms. There are localized edema and hyperemic patches which break down to form ulcers with irregular borders and which are covered with yellowish-gray sloughs. When the slough is removed there remains a raw bleeding surface. The infection may extend to the larynx, eustachian tubes, and middle ear. There may be general malaise, low-grade fever, and occasionally a regional lymphadenitis. The lesion produces a disagreeable taste and a fetid breath.

Cancrum Oris or Noma.—This is a rapidly spreading gangrenous inflammation of the mucous membrane of the mouth which is usually fatal. It occurs most frequently in institutionalized and malnourished children, especially following exanthematous fevers. The area in-

volved is grayish-black in color and the necrotizing inflammation may extend to the underlying bones.

Genital Fusospirochetosis.—This is sometimes called the fourth venereal disease. While secondary infections are more common, primary fusospirochetosis may occur, especially in males. The usual sites of primary fusospirochetal lesions are the glans and mucosal surface of the prepuce. Pronounced hyperemia and small superficial ulcers with circinate edges covered with a grayish-white membrane and exuding a copious yellow, frothy, fetid discharge are characteristic signs. The lesions may coalesce and become excessively destructive.

The lesions of secondary fusospirochetosis are similar to those of the primary infection and frequently obscure the underlying process. It is necessary to treat the fusospirochetosis as well as the underlying disease to obtain satisfactory results. In both male and female, secondary fusospirochetosis is common, involving 12 per cent of all ulcerative pudendal lesions.

Pulmonary Fusospirochetosis.—Bronchiectasis, abscess, gangrene, and pneumonia have been attributed to primary infection with the fusospirochetes. Acute and chronic forms of pulmonary spirochetosis have been reported as a common disease in the orient and clinically are difficult to distinguish from tuberculosis. Parenchymal necrosis and extensive cavitation occur. Pulmonary fusospirochetosis may result from aspiration, especially as a postoperative complication. Abscesses may result and extensive gangrene may prove rapidly fatal. Putrid empyema is a frequent complication.

In many bronchiectatic cavities of whatever cause, fusospirochetes may be found as saprophytes in the debris. The organisms may at any time assume pathogenicity and then cause progressive necrosis with pseudomembranous formation, and excavation may proceed rapidly and gangrene result. When cavities are infected with fusospirochetes the patients will usually have a moderate fever and leukocytosis. Coughing is a symptom and the expectoration is fetid, grayish-brown, or blood-streaked.

Microscopic Pathology

In all fusospirochetal diseases the organisms are demonstrable in abundance in stained films. The spirochetes predominate. The microscopic changes are similar in all lesions. Spirochetes and fusiform bacilli are commonly found in the detritus of many lesions of the mouth and genitals; however they may not necessarily contribute to the pathologic changes found in the lesion, and are then only saprophytic. Therefore, the demonstration of the organisms by films or in detritus histologically does not infer fusospirochetosis. When they become pathogenic, a necrotizing inflammation results. Superficially there is liquefaction necrosis and resulting ulceration. The upper surface of the ulcer is a mass of necrotic debris in which are entangled a number of fusiform bacilli and spirochetes and a multiplicity of secondary invaders. Underlying the superficial zone of necrosis and cell detritus, there is a narrow zone of reaction in-

filtrated with polymorphonuclear leukocytes and lymphocytes. The polymorphonuclear leukocytes emigrate toward the surface and are quickly converted into debris. The spirochetes are more numerous in the deeper necrotic layer and penetrate slightly into the reaction zone. Thrombosis of the vessels inhibits the formation of healthy granulation tissue. At the margins there is intraepithelial and subepithelial edema with organisms present in the epithelium. In neglected lesions, necrosis progresses and mutilation results. When adequately treated, the superficial lesions heal without scar formation.

CHANCROID

Chancroid (chancre mou, ulcus molle, soft chancre) is an acute ulceration usually of venereal origin and therefore most commonly found on or near the genitals.

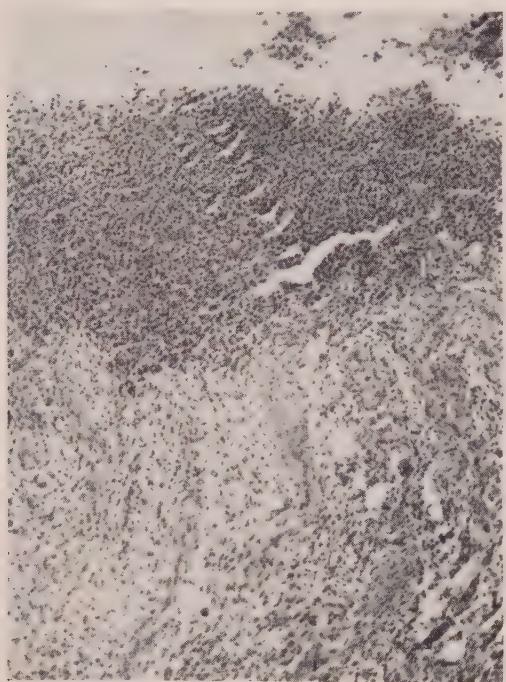


Fig. 190.—Histologic section of chancroid. Note the three ill-defined zones and the perivasculitis and endovasculitis in the second zone.

It is a highly infectious disease with a short incubation period and is auto-inoculable; therefore, multiple lesions are common. The ulcers are usually found on the prepuce, corona, and shaft of the penis in males, and on the labia minora, clitoris, fourchette, and vestibule in females. The cervix and vaginal wall are not uncommon sites for chancroids. In these locations spontaneous healing, with-

out bubo formation, probably accounts for the reported prevalence of chancroid infection in males and the postulation of saprophytic infestation of the vagina. Primary or secondary lesions may occur on the scrotum in males and on the thighs and anal orifice in both sexes. Extragenital lesions on fingers, lip, and tongue are infrequent. Like many of the venereal diseases, it is usually one of filth and neglect.

Distribution.—Chancroids are observed in all parts of the world; the incidence varies directly with the degree of promiscuity and uncleanliness. In this country it is more common in Negroes than in white persons.

Cause.—The causative organism was described by Ducrey in 1889. *Hemophilus ducreyi* is a gram negative, short, nonmotile bacillus with rounded ends, 1 to 2 microns long and 0.5 micron thick, which occurs in rods, pairs, or chains.

Clinical Course.—The moderately painful and tender ulcer appears after an incubation period of three to ten days. Within ten to twenty days a painful unilateral or bilateral inguinal adenitis occurs in 40 per cent of cases, especially in those with inadequate drainage of the primary ulcer. The adenitis is usually accompanied by fever, anorexia, malaise, and leukocytosis.

Clinical Appearance of the Ulcer.—The ulcer begins as a small reddish macule which becomes papular, then pustular, and finally ulcerates. It is circinate or ovoid, with friable, soft, ragged, irregular, undermined borders. The base is dirty, uneven from alternating elevations and depressions, bleeds readily, and is covered with yellow-gray purulent exudate. At first the ulcer is shallow, from a few millimeters to 1 or 2 cm. in diameter, and enlarges by peripheral extension. Transient, dwarf, follicular, giant, and phagedenic forms are described.

Histopathology.—At the site of inoculation the epithelial cells are swollen and edematous and beset with a number of polymorphonuclear leukocytes. A small epidermal abscess develops, and the overlying epithelium becomes necrotic and sloughs. In the corium the lymph and blood vessels are dilated and surrounded by polymorphonuclear leukocytes, lymphocytes, and a few plasma cells. In the fully developed ulcer there are three poorly defined zones. There is a superficial, compact layer of pyknotic and karyorrhectic polymorphonuclear leukocytes, fibrin, red blood cells, and necrotic tissue, which dips downward into the irregular clefts of the granulation tissue of the second zone. The granulation tissue is edematous and infiltrated with polymorphonuclear leukocytes, lymphocytes, and macrophages. The polymorphonuclear leukocytes are especially numerous within and around the capillaries; the endothelial cells are swollen, and granular thrombi may be found in the lumina. The tips of many of the capillaries are necrotic and terminate in the first zone. The endovasculitis and perivasculitis is the most characteristic feature of the histologic picture. This inflammatory reaction extends beneath the

bordering epithelium and is the cause of the undermined edges of the ulcer. This zone is not sharply delimited and is continuous with a third zone of dense plasma cell and lymphocytic infiltration especially perivascular in distribution.

The lymph nodes are congested, edematous, and hyperplastic, and there is a disseminated polymorphonuclear leukocytic infiltration. The inflammatory exudate involves the edematous capsules. A perivasculitis and endovasculitis are prominent features, especially when abscesses develop. The abscess is usually unilocular and involves several confluent nodes, the coalescence being due to the intense perilymphadenitis. The wall of the abscess is similar in histologic appearance to the chancroidal ulcer.

GRANULOMA VENEREUM

Granuloma venereum (granuloma inguinale; pudenda tropicum) is a chronic specific granulomatous infection, chiefly of the skin and subcutaneous tissues. The lymph nodes are rarely noticeably involved. The proclivity of the disease for the external genitals has earned it a place in the category of venereal diseases. Ulcerative lesions may be present for years with little inconvenience to the patient, and the prognosis as to life is

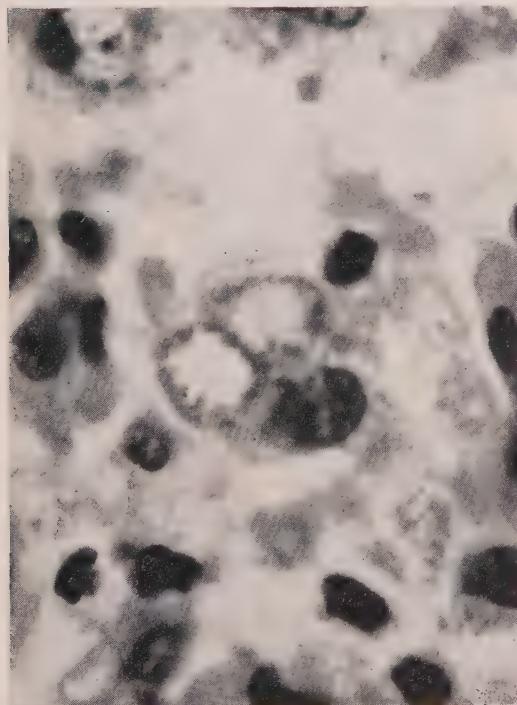


Fig. 191.—Granuloma venereum (inguinal). (H. & E., $\times 2230$.) Note the macrophage in center which contains two intracytoplasmic cysts with the Donovan bodies in the periphery. (Courtesy Am. J. Surg. 44: 552, June, 1939.)

good, but it may often be disabling and is sometimes fatal. While the infrequency of the infection in the coital partner lends some doubt as to its venereal nature, it is more probably evidence of its mild contagiousness. The lesions are commonly mixed with those of other kinds of venereal disease, which predispose the individual to this infection. Individual susceptibility, uncleanliness, and race play causative roles.

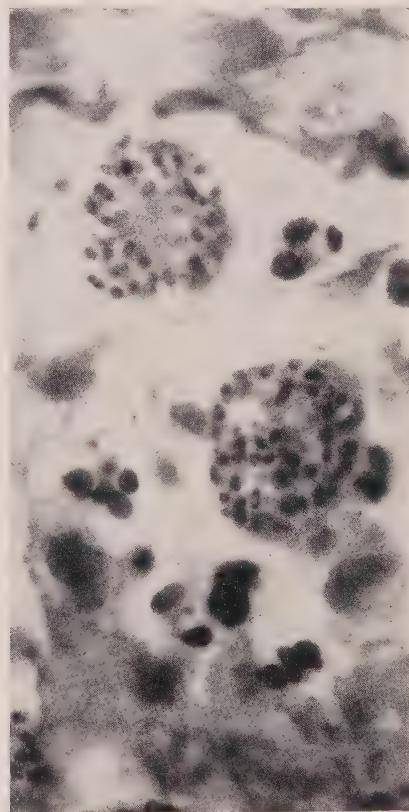


Fig. 192.—Granuloma venereum (inguinal). (Dieterle's silver stain, $\times 1900$.) The Donovan bodies within the macrophages stain with silver. Because of the bipolar staining, the "closed safety pin" appearance is observed in many. With this stain, the cysts are not easily seen. (Courtesy Am. J. Surg. 44: 552, June, 1939.)

Ulcerations most frequently occur on the external genitals and in the inguinal region. The inguinal ulcers may be primary but are usually secondary to genital lesions which spread to the inguinal region either by continuity, autoinoculation, or through the lymphatics. The perineum, inner thighs, perianal region, anus, abdomen, vagina, cervix, urethra, bladder, and rectum may be involved primarily, or secondarily by contiguity. Exogenous lesions are observed in 6 per cent of cases, usually as a result of transfer

of the infection from the genitals, and rarely as a nonvenereal disease. Lesions occur in the skin in various parts of the body and on the mucous membrane of the lips, oral cavity, pharynx, esophagus, and larynx. The demonstration of the involvement of lymph nodes lends support to the theory of lymphatic spread and explains the frequency of inguinal involvement, especially when the ulceration is preceded by a pseudobubo. The infection may extend from the cervix to the body of the uterus, to the tubes and ovaries, particularly after delivery or abortion. Metastatic hematogenous infections of the subcutaneous tissue, bones, and joints have been reported.

Systemic symptoms such as fever, anemia, loss of weight, malaise, and mild leukocytosis are observed only in extensive infections.

Cause.—Donovan, in 1904, described the organism which bears his name, although the disease had been recognized as a clinical entity by McLeod in India in 1882. The Donovan bodies are found either free or in macrophages in films and in histologic sections from the lesions. They occur as single, small, nubby condensations or bipolar condensations of chromatin with a bacillary body surrounded by a well-defined capsule. Intracellularly the bodies are found in intracytoplasmic cysts. They are gram negative. They were first cultivated by Anderson, de Monbreun, and Goodpasture in 1943 and were considered as facultative intracellular parasites, probably bacterial and bacillary, and the name *Donovania granulomatis* was suggested. Antigens which elicit reactions in the skin and serum of patients have been produced. The organism has also been cultivated *in vitro*. The disease has been produced by inoculation experiments on human beings, and the incubation period was found to be 35 to 40 days.

Distribution.—The disease is more prevalent in tropical and subtropical climates but may be found anywhere. It occurs at the age of active sex life and flourishes in a strata of society where soap and water and straight-laced morals are not considered a necessity of life. In this country it is far more common in Negroes.

Clinical Appearance of Ulcer.—The lesion begins as a papule which becomes vesicular and pustular or as a nodule 1 to 4 cm. in diameter. Ulceration ensues and the typical ulcer develops by peripheral extension. The clean, raised tuft of velvety, beefy-red granulation tissue with well-defined borders is characteristic; the advancing border has rolled margins due to the granulation tissue piling over the border. Multiple papules and nodules may run a similar course and coalesce to form a large ulcer. Extension along the lymphatics of the skin may produce satellite ulcers, and secondary ulcers may result from autoinoculation. The ulcers may continue to enlarge and develop into a hypertrophic form, and the exuberant nodules of granulation tissue form a cerebriform surface. In these the underlying fibroblastic reaction goes hand in hand with the progressive ulceration, so that the lesions resemble a bas-relief map of mountainous country. The fibroblastic reaction may continue with some healing, and a firm, elastic, partly ulcerated, keloid-like lesion of knolls and depressions is formed. The

lesions are described as nodular, ulcerovegetative, hypertrophic, and cicatricial. Blockage of the lymphatics may lead to elephantiasis. When secondary infection occurs, especially with fusospirochetes, deep ulceration results from rapid spread and excavation. Under treatment the ulcers heal and leave an atrophic depigmented scar. The inguinal ulcers are frequently secondary to genital infections and develop from a subcutaneous, soft, fluctuant swelling known as a pseudobubo.

Gross Appearance of Visceral Lesions.—When the uterus, tubes, and ovaries are involved, they are symmetrically enlarged. The myometrium, tubal wall, and ovaries appear moist and fibrous with scattered minute yellow foci of suppuration. The diffuse enlargement of the ovaries may simulate a solid tumor. The endometrium may be ulcerated. The rarely involved lymph nodes are slightly enlarged and appear firm and grayish-white.

Histopathology.—In the papulonodular stage there is hypertrophy of the epithelium with elongation of the rete pegs, edema of the papillae, and the corium is infiltrated with polymorphonuclear leukocytes and macrophages, many of which contain the organisms. Ulceration follows and plasma cells become increasingly prominent. The ulcer of granuloma venereum in the pure or unmixed form reveals a uniform histologic picture. The essential features are: (a) massiveness of the cellular reaction in which the luxuriant granulation tissue is charged with plasma cells; (b) the relative and conspicuous paucity of lymphocytes; (c) the diffuse sprinkling of polymorphonuclear leukocytes with focal collections in the superficies and bordering papillae; (d) the marginal epithelial proliferation with elongation of the rete pegs; and (e) the presence of pathognomonic large mononuclear cells scattered in various numbers throughout the granulation tissue and especially numerous in the superficies, in the papillae, and in the clusters of polymorphonuclear leukocytes. As fibrosis takes place, nests of plasma cells, few polymorphonuclear leukocytes, and occasional macrophages laden with parasites are observed in the interstices of the new-grown connective tissue. The pathognomonic cell is a large mononuclear cell, 25 to 90 microns in diameter, which contains intracytoplasmic cysts filled with the Donovan bodies. There may be a single cyst or as many as ten. The Donovan bodies are round or rodlike bodies which stain purplish with hematoxylin and eosin and are usually distributed peripherally within the cysts. The nucleus of the macrophage is crowded to one side and is often pyknotic. The affinity of the intracytic bodies for silver salts facilitates the recognition of the characteristic cell. The bodies stain brown to black and have a "safety-pin" appearance because of the bipolar staining and their ovoid shape. The bodies may be demonstrated in frozen sections stained with polychrome methylene blue.

When the uterus is involved, there occurs ulceration and granulation of the cervix and endometrium, with an inflammatory reaction similar to that described above. There is also dissociation of the muscle bundles by an exudate

of plasma cells, groups of polymorphonuclear leukocytes and macrophages, many of which contain the Donovan bodies. The groups of polymorphonuclear leukocytes may constitute minute abscesses. There is associated fibroblastic activity and capillary proliferation. The tubes and ovaries present a similar picture. In the involved lymph nodes, the lymphocytes are largely replaced by plasma cells, polymorphonuclear leukocytes, macrophages, many of which are laden with Donovan bodies, and fibroblasts. The metastatic bone lesions have been described as a lytic reaction without sequestrum formation.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (lymphogranuloma inguinale, lymphopathia venereum) is an infectious disease caused by a filtrable virus and is usually transmitted by sexual intercourse. It therefore belongs in the category of venereal diseases. Children may be innocently infected, usually through the urethra, and rarely physicians and nurses may acquire the disease accidentally.

Lymphogranuloma venereum is primarily a disease of a local unit of the lymphatic system and its surrounding connective tissue. It may occur (a) as an acute, self-limited disease or (b) as a chronic infection of several years' duration. The acute form is the "primary-bubo complex," which was recognized by Durand, Nicolas, and Favre in 1913 and described in this country by Hansmann in 1924. This complex, which occurs more commonly in males than in females, may confer a lasting immunity, and the individual is often spared other consequences. Generalized dissemination of the virus, in the acute phase, produces characteristic systemic symptoms. Rarely, metastatic hematogenous lesions may result, and involvements of the brain and meninges, lungs, kidneys, joints, bones, pericardium, and conjunctiva have been reported.

The chronic manifestations may begin as such at the site of inoculation, usually without bubo formation, or, after a period of latency of varying length, chronic lesions may result from reactivation of the virus at previous sites of infection. The local chronic lesions are characterized by a progressive lymphangitis which produces chronic edema and sclerosing fibrosis. Genital elephantiasis, esthiomene, and anorectal, vaginal, and urethral strictures with formation of sinuses and fistulas are the most frequent chronic lesions.

Cause

The causative virus was discovered by Hellerström and Wassen in 1930. The virus has been propagated in various laboratory animals and cultivated on the allantoic membrane and yolk sac of the chick embryo. Cytoplasmic inclusion bodies have been observed in the cells of the chick embryo and in inflam-

matory cells of human and experimental animal lesions. The virus has been recovered from the primary ulcer, inguinal bubo, labial tissues in esthiomene, rectal, urethral, and cervical mucosa, conjunctival exudates, spinal fluid, and blood. Antigenically it resembles that of the psittacosis group, which includes the viruses of trachoma, atypical pneumonia, inclusion blenorhea, pneumomeningitis, and feline pneumonitis.

The virus is probably disseminated by the blood and lymph from the site of inoculation and in most instances is quickly destroyed except in the region local to the site of primary inoculation. Rarely the disease is manifest as a systemic infection with generalized lymphadenopathy. A single attack probably confers a lasting and effective immunity. Virucidal antibodies have been demonstrated in the serum of the blood and a specific complement fixation test has been developed.

The reaction to the intradermal inoculation of killed virus offers a means of diagnosis and is known as the Frei test. The yolk sac of the chick embryo has proved to be a more convenient and better source for preparation of the antigen than bubo pus as originally used by Frei. A positive Frei test develops in two to six weeks after the occurrence of the primary lesion and remains positive for years, even after the disease has become latent or quiescent. The infectiousness of patients with a positive Frei test and without clinical manifestations is suggestive, but has not been definitely determined. The complement fixation test may be positive in newborn babies of infected mothers, but the reaction disappears in two to four months.

Distribution

Lymphogranuloma venereum is found in all parts of the world, but it is more common in places with warm climates and is more prevalent during the warmer seasons. It occurs frequently in individuals with promiscuous sexual habits and in those with an aversion to soap and water. In this country the incidence of positive Frei reactions has been recorded as high as 40 per cent of Negro and 3.4 per cent of white adults.

The Primary-Bubo Complex

The course and manifestations of the disease depend upon the site of inoculation. A primary sore develops at the site after an incubation period of 3 to 21 days, usually within 7 to 12 days. In the male the primary generally appears on the penis and occasionally in the urethra, and the usual sites in the female are the cervix, vulva, and vagina, especially at the fourchette or on the posterior vaginal walls.

At sites where secondary infections are not likely to occur, the primary lesion is followed by a regional lymphadenitis, and this constitutes the primary-bubo complex. This is obviously more common in males than females. On the external genitals the primary lesion may be a papule, a small herpetiform lesion, or a superficial ulcer. The ulcer, the most common lesion, is painless, remains as a small clear-cut erosion without induration, and heals spontaneously within a few days with little scarring.



Fig. 193.—Section of inguinal bubo of lymphogranuloma venereum. Multiple abscesses



Fig. 194.—Section of inguinal bubo of lymphogranuloma venereum. Collection of nuclear debris surrounded by macrophages.

Histopathology of the Primary.—The lesion is characterized by hyperplasia of the epithelium and elongation of the rete pegs. The epithelial cells undergo hydropic degeneration and there is intraepithelial edema. In the subepithelial connective tissue there is a well-defined zone of plasma cells and macrophages. The infiltrate streams along the perivascular and perineurial lymphatics. In the zone of infiltrate the endothelial cells of the hyperplastic capillaries are swollen. Polymorphonuclear leukocytes accumulate in the superficies of the ulcer.

The Bubo.—An inguinal and iliac lymphadenitis follows the evanescent primary genital lesion within two to eight weeks and is bilateral in 35 per cent of the cases. Similar buboes may develop in the regional nodes which drain other primary lesions—a axillary from the hand, cervical from the mouth and conjunctiva. The nodes enlarge and, because of the perilymphadenitis, soon form a conglomerate mass of considerable size. The overlying skin becomes tense and violaceous in color. The femoral nodes are often involved with the ilio-inguinal, and the inguinal ligament characteristically grooves the mass. Multiple areas of fluctuation are palpable when abscesses develop. Ulceration and multiple sinus formation results from spontaneous rupture or surgical incision. Resolution may occur at any stage, and one-third resolve without ulceration. The duration of the adenitis is from ten days to three months.

Grossly the lymph nodes are enlarged, conglomered, granular, and purplish-pink in color. Abscesses appear as discrete and confluent moist yellow foci which have a tendency to appear stellate.

Histopathology of the Bubo.—A diffuse lymphocytic and reticuloendothelial hyperplasia precedes an infiltration of plasma cells throughout the node. Macrophages accumulate in discrete foci, and, as the foci enlarge, the centers undergo necrosis and polymorphonuclear leukocytes accumulate and disintegrate. The marginal macrophages assume a palisade arrangement and surround the central area of cellular debris. Proximate foci become confluent and the typical stellate abscesses result. An occasional macrophagic giant cell may be seen, particularly in the margin of the abscesses. Fibroblasts proliferate around the abscesses in the later stages. The capsules of the nodes are edematous, congested, and infiltrated with plasma cells and lymphocytes, which are especially numerous about the blood vessels and the

dilated lymph vessels. As the abscesses resolve, they are replaced by fibrous connective tissue.

The Chronic Lesions

When the primary lesion occurs at sites which are subjected to secondary infection, a protective bubo is less likely to develop and the lesion may assume chronicity from the start. In the male, the primary lesion commonly occurs on the penis; whereas, in the female the inner surface of the vulva, the vagina, and the cervix are the most frequent sites, areas in which the initial ulcer is subjected to secondary infections and to maceration. In the female, too, the lymphatic drainage of the deeper portions of the vagina and cervix is partly to the perirectal lymph nodes. For these reasons chronic lesions are far more frequently encountered in the female. Chronic lesions may also occasionally develop after a variable period of latency of the infection in patients who have apparently recovered with or without bubo formation. This results from reactivation of the virus at the site of inoculation. The time of onset of chronic lesions may therefore vary from six weeks to ten years after the initial infection.

Esthiomene, Elephantiasis Vulvae, and Vaginal Stricture.—Genital lesions are frequent chronic manifestations of lymphogranuloma venereum in the female. Chronic edema and fibrosis of the vagina leads to stricture and of the vulva to elephantiasis. The wall of the vagina becomes rigid, especially posteriorly, and chronic shallow ulcers are present. In elephantiasis vulvae, the labia enlarge and the folds between the labia minora and majora disappear. The clitoris is commonly involved and may enlarge to the size of a penis. The skin and mucous membrane of the vulva may remain smooth, but frequently the surface becomes irregularly nodular, scaly, and covered with warty polypoid excrescences, or is irregularly corrugated. One or more chronic ulcers are invariably present and weeping ulcers are prone to occur because of lymph stasis. This condition is known as esthiomene. Cervical infection may rarely be followed by involvement of the tubes.

Penile Elephantiasis.—Elephantiasis of the entire penis and scrotum is infrequent, although elephantiasis of the prepuce is not uncommon. This results from the presence of a persistent primary ulcer on the glans or undersurface of a redundant prepuce. The prepuce is greatly thickened, phimosis occurs, and balanoposthitis results, with sinus and fistula formation. Nodular extension along the lymphatics of the shaft of the penis leads to the formation of bubonitis.

Anorectal Disease.—The anorectal mucous membrane may be the site of the primary lesion in males who are addicted to coitus analis, and a chronic proctitis followed by stricture may result. By the lymphatic route, the infection may spread to the rectum in males from the posterior urethra.

In the female, anorectal inflammatory changes are almost always secondary and are frequent and serious manifestations. There are three



Fig. 195.—Section of elephantiasic vulva in lymphogranuloma venereum. Thromboendolymphangitis.

possible routes of extension from the involved genitals. The most probable route is direct extension from the vagina through the rectovaginal septum. The involvement of the anorectum is frequently accompanied by rigidity and firmness of the posterior vaginal wall. Second, because of the lymphatic anastomoses, the infection may extend from the deeper portion of the vagina and from the cervix to the perirectal lymph nodes of Gerota, which lie in the perirectal fat. Third, the virus may be transferred from the vulva to the anorectal mucosa because of the continuity of vulva and anus.

The first sign of anorectal involvement, especially in the male, may be proctitis which is characterized by a mucopurulent discharge, polypoid hyperplasia of the mucosa, and shallow ulceration. A stricture invariably follows untreated proctitis. The stricture, which may be bandlike or tubular, is usually found within 6 cm. of the anal orifice. The wall of the affected bowel is thickened, fibrous, and rigid, and the mucosa is ulcerated and covered by a thin layer of granulation tissue. Perianal cauliflower excrescences of variable size frequently encircle the anal orifice and are known as lymphorrhoids. Sinuses and rectal and rectovaginal fistulas are prone to develop and, in instances of urethral involvement, urethrovaginal fistulas as well.

Alternating bouts of constipation and diarrhea, painful defecation, and sensation of full-

ness are the usual symptoms of anorectal stricture. Secondary anemia is not uncommon.

Histopathology of the Chronic Lesions.—The microscopic appearance of the secondary manifestations is similar for all sites. The histologic lesions are nonspecific and not as distinctive as the gross appearance. The chief features of the inflammatory process are chronic ulcers, thromboendolymphangitis, edema, fibrosis, focal abscesses, and fistula formation. The chief cell of the infiltrate is the plasma cell.

Persistent ulcerations are characterized by granulation tissue densely infiltrated with plasma cells, lymphocytes, and macrophages. The number of polymorphonuclear leukocytes varies directly with secondary infection and the cells are distributed superficially. In the early phase of ulceration spherical foci of macrophages and giant cells may be observed in the deeper portions of the granulation tissue and in the underlying fibrous tissue. The absence of caseation distinguishes these pseudotubercles from the tubercles of tuberculosis. There is a widespread perivascular and perineural infiltration of plasma cells and lymphocytes throughout the expanse of edematous connective tissue. The lymph vessels are distended and, in many, the lymph is coagulated; the lining endothelial cells are swollen. The progress of the inflammatory reaction can be followed through the trabeculations of connective tissue in the surrounding muscle of the anorectum, vagina, and urethra. Pseudotubercles occur indiscriminately

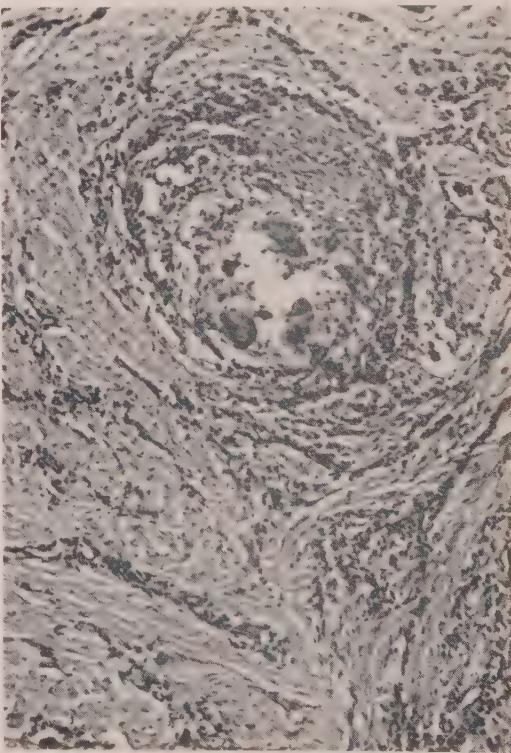


Fig. 196.—Section of elephantiasic vulva in lymphogranuloma venereum. Pseudotubercle formation.

in the active inflammatory phase. Scattered foci of macrophages surrounding disintegrated polymorphonuclear leukocytes may be observed. These foci may coalesce and progress to sinus and fistula formation. As fibrosis progresses the infiltrate diminishes and the pseudotubercles disappear. Elephantiasis of the external genitals and lymphorrhoids of the anus result from lymph stasis, edema, and fibrosis. Contraction of new-formed connective tissue produces strictures of the tubular structures—anorectum, vagina, and urethra—and hypertrophy of the muscles ensues. The irregularity of the surface of the elephantiasic genitals and the anal tabs also results from contraction. Secondary superficial ulceration results from the lymph stasis. The stratified squamous epithelium overlying the vulval, anal, and penile lesions is hyperplastic, acanthotic, and it is not unusual to observe a degree of anaplasia. A disproportionate number of carcinomas of the external genitals and anal orifice originate in the chronic lesions of lymphogranuloma venereum.

Superimposed chancroids, ulcers of granuloma venereum, and secondary infection with fusospirochetes often confuse the histologic picture.

References

Syphilis

- Auerbach, S. H.: Ann. Int. Med. 22: 870, 1945.
 Becker, S. W.: M. Clin. North America 26: 65, 1942.
 Beerman, H., Wammock, V. S., and Magnuson, K. B.: Am. J. Syph., Gonor. & Ven. Dis. 26: 504, 1942.
 Black-Schaffer, B., and Rosahn, P. D.: Am. J. Syph., Gonor. & Ven. Dis. 28: 27, 1944.
 Braunstein, A. L., Bass, J. B., and Thomas, S.: Am. Heart J. 19: 613, 1940.
 Crawford, G. M.: New England J. Med. 232: 76, 1945.
 Crawford, G. M.: New England J. Med. 232: 107, 1945.
 Davison, C., and Kelman, H.: Arch. Neurol. & Psychiat. 38: 43, 1937.
 Dippel, A. D.: Am. J. Obst. & Gynec. 47: 369, 1944.
 Evans, N.: Arch. Path. 37: 175, 1944.
 Ferris, H. W., and Turner, T. B.: Arch. Path. 24: 703, 1937.
 Francis, H. C., and Kampmeier, R. H.: South. M. J. 36: 556, 1943.
 Gordon, W. H., Parker, F., Jr., and Weiss, S.: Arch. Int. Med. 70: 396, 1942.
 Hahn, R. D.: Am. J. Syph., Gonor. & Ven. Dis. 27: 529, 1943.
 Hejtmancik, M. R., Bradfield, J. V., and Rigdon, R. H.: Am. J. Syph., Gonor. & Ven. Dis. 34: 236, 1950.
 Herman, M., and Rosenblum, M. P.: Am. J. Psychiat. 96: 1311, 1940.
 Heyman, A., and Brown, C. E.: Ann. Int. Med. 25: 728, 1946.
 Hinrichsen, J.: Am. J. Syph. Gonor. & Ven. Dis. 27: 319, 1943.
 Hopkins, H. H.: Bull. Johns Hopkins Hosp. 49: 5, 1931.
 Kalz, F., and Ereaux, L. P.: Clinics 3: 133, 1944.
 Kalz, F., and Newton, B. L.: Arch. Dermat. & Syph. 48: 626, 1943.
 Katz, S., Hussey, H. H., and Walsh, B. J.: Ann. Int. Med. 22: 606, 1945.
 Klauder, J. V., Meyer, G. P., and Gross, B. A.: Am. J. Syph., Gonor. & Ven. Dis. 38: 574, 1948.
 Kolmer, J. A.: New Orleans M. & S. J. 97: 335, 1935.
 Kuhl, I. W., and Briggs, H.: New England J. Med. 238: 399, 1948.
 Lovemen, A. B., and Morrow, R. P., Jr.: Am. J. Syph., Gonor. & Ven. Dis. 28: 44, 1944.
 McCord, J. R.: J. A. M. A. 88: 626, 1927.

- Meiman, B. H., and Marks, M. B.: Am. J. Dis. Child. 59: 571, 1940.
 Perry, W. L. M.: J. Path. & Bact. 60: 339, 1948.
 Pratt-Thomas, H. R.: Arch. Path. 36: 80, 1943.
 Pund, E. R., and Brawner, G. H.: Ann. Otol., Rhin., & Laryng. 44: 984, 1935.
 Reynolds, F. W.: Am. J. Syph., Gonor. & Ven. Dis. 26: 218, 1942.
 Reynolds, F. W., and Wasserman, H.: Arch. Int. Med. 69: 263, 1942.
 Rosahn, P. D., and Black-Schaffer, B.: Yale J. Biol. & Med. 15: 587, 1943.
 Saphir, O.: Am. J. Path. 5: 397, 1929.
 Sarnat, B. G., Schour, I. S., and Heupel, R.: J. A. M. A. 116: 2745, 1941.
 Sarnat, B. G., and Shaw, N. G.: Am. J. Dis. Child. 64: 771, 1942.
 Shaw, C.: Arch. Dermat. & Syph. 42: 456, 1940.
 Spain, D. H., and Johannsen, M. W.: Am. Heart J. 24: 689, 1942.
 Sohval, A. R.: Arch. Path. 20: 429, 1935.
 Soloway, H. M.: J. A. M. A. 129: 500, 1945.
 Stone, S.: Arch. Ophth. 30: 467, 1943.
 Symmers, D., and Spain, D. M.: Arch. Path. 42: 64, 1946.
 Turner, T. B.: Bull. Johns Hopkins Hosp. 46: 159, 1930.
 Tuta, J. A., and Coombs, R. A.: Arch. Dermat. & Syph. 46: 375, 1942.
 Warthin, A. S.: New York Med. J. 115: 69, 1922.
 Warthin, A. S.: Am. J. Syph. 2: 425, 1918.
 Wile, U. J., and Mundt, L. K.: Am. J. Syph., Gonor. & Ven. Dis. 26: 70, 1942.
 Williams, C., and Kimmelstiel, P.: J. A. M. A. 115: 578, 1940.
 Wilson, J. S.: Ann. Int. Med. 25: 134, 1946.
 Woods, A. C.: Am. J. Syph., Gonor. & Ven. Dis. 27: 133, 1943.
 Yampolsky, J., and Powell, C. C.: Am. J. Dis. Child. 63: 371, 1942.
 Yong, K. L.: Arch. Dermat. & Syph. 41: 1060, 1940.

Faws

- Blalock, D. B.: Ann. Trop. Med. 26: 423, 1932.
 Butler, C. S.: Mil. Surgeon 78: 174, 1936.
 Chambers, H. D.: J. A. M. A. 124: 667, 1944.
 Choisser, R. M.: U. S. Nav. M. Bull. 27: 551, 1929.
 Ferris, H. W., and Turner, T. B.: Arch. Path. 24: 703, 1937.
 Ferris, H. W., and Turner, T. B.: Arch. Path. 28: 491, 1938.
 Fox, H.: Arch. Dermat. & Syph. 6: 657, 1922.
 Fox, H.: Arch. Dermat. & Syph. 20: 820, 1929.
 Fox, H.: J. A. M. A. 123: 459, 1943.
 Goodman, H.: Am. J. Syph. 10: 64, 1926.
 Gutierrez, P. D.: Arch. Dermat. & Syph. 12: 159, 1925.
 Gutierrez, P. D.: Arch. Dermat. & Syph. 12: 465, 1925.
 Gutierrez, P. D.: Arch. Dermat. & Syph. 8: 382, 1933.
 Kumm, H. W., and Turner, T. B.: Am. J. Trop. Med. 16: 245, 1936.
 MacLeod, J. M. A.: Brit. M. J. 2: 797, 1901.
 Nichols, H. J.: Am. J. Trop. Med. 5: 429, 1925.
 Pardo-Castello, V.: Arch. Dermat. & Syph. 40: 762, 1939.
 Saunder, G. M., and Meunch, H.: Am. J. Hyg. 26: 423, 1937.
 Schamburg, J. F., and Klauder, J. V.: Arch. Dermat. Syph. 3: 49, 1921.
 Turner, T. B.: Am. J. Hyg. 25: 477, 1937.
 Turner, T. B., and Chesny, A. M.: Bull. Johns Hopkins Hosp. 54: 174, 1934.
 Turner, T. B., and McLeod, C.: Tr. A. Am. Physicians 57: 265, 1943.
 Weller, C. V.: Am. J. Syph., Gonor. & Ven. Dis. 20: 467, 1936.
 White, C. J., and Tyzzer, E. E.: J. Cut. Dis. 29: 138, 1911.
 Whitehead, R., and Austrian, R.: Bull. Johns Hopkins Hosp. 75: 232, 1944.
 Idem: Bull. U. S. Army M. Dept. 86: 84, 1945.
 Williams, H. V.: Arch. Path. 20: 596, 1935.
 Wilson, P. W.: Am. J. Trop. Med. 14: 1, 1934.
 Wilson, P. W., and Mathis, M. S.: J. A. M. A. 94: 1289, 1930.

Bejel

- Hasselmann, C. M.: Arch. Dermat. & Syph. 38: 837, 1938.
 Hudson, E. H.: Am. J. Syph. 16: 447, 1932.

- Hudson, E. H.: Am. J. Syph. **17**: 10, 1933.
 Hudson, E. H.: Ann. Int. Med. and Parasitology **30**: 3, 1936.
 Hudson, E. H.: Arch. Dermat. & Syph. **33**: 994, 1936.
 Hudson, E. H.: New England J. Med. **215**: 392, 1936.
 Hudson, E. H.: Am. J. Syph., Gonor. & Ven. Dis. **21**: 45, 1937.
 Hudson, E. H.: Am. J. Trop. Med. **18**: 675, 1938.
 Rost, G. S.: Radiology **38**: 320, 1942.
- Pinta*
- Beerman, H.: Am. J. M. Sc. **205**: 611, 1943.
 Editorial: Arch. Dermat. & Syph. **39**: 709, 1939.
 Editorial: J. A. M. A. **126**: 1030, 1944.
 Fox, H.: Arch. Dermat. & Syph. **18**: 673, 1928.
 Fox, H.: J. A. M. A. **123**: 459, 1943.
 Holcomb, R. C.: U. S. Nav. M. Bull. **40**: 517, 1942.
 Lieberthal, E. P.: J. A. M. A. **123**: 619, 1943.
 Pardo-Castello, V., and Ferrer, I.: Arch. Dermat. & Syph. **45**: 843, 1942.
 Saenz, B., Grau Triana, J., and Armenteros, J. A.: Arch. Dermat. & Syph. **41**: 463, 1940.
 Varela, G., and Avila, C.: Am. J. Trop. Med. **27**: 663, 1947.
- Weil's Disease*
- Alston, J. M., and Broom, J. C.: Brit. M. J. **2**: 718, 1944.
 Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W.: Medicine **20**: 145, 1941.
 Baehr, G., and Klemperer, P.: J. Mt. Sinai Hosp. **9**: 971, 1943.
 Beeson, R. B., Hankey, D. D., and Cooper, C. F., Jr.: J. A. M. A. **145**: 229, 1951.
 Bulmer, E.: Brit. M. J. **1**: 113, 1945.
 Campbell, A. M. G., MacCrae, J., Manderson, W. G., Sumner, K. C., and Broom, J. C.: Brit. M. J. **1**: 336, 1950.
 Carragher, A. E.: Brit. M. J. **1**: 119, 1945.
 Clapper, M., and Meyers, G. B.: Arch. Int. Med. **72**: 18, 1943.
 Cross, R. M.: Lancet **1**: 211, 1945.
 Davidson, L. S. P., and Smith, J.: Brit. M. J. **2**: 753, 1939.
 Fine, J. M., and Conen, W. J.: Wisconsin M. J. **42**: 408, 1943.
 Grell, O.: Schweiz. med. Wochenschr. **76**: 237, 1946.
 Harris, W. H., Jr.: Arch. Path. **34**: 663, 1942.
 Jeghers, H. J., Houghton, J. D., and Foley, J. A.: Arch. Path. **20**: 447, 1935.
 Larson, C. L.: Pub. Health Rep. **58**: 949, 1943.
 Larson, C. L.: U. S. P. H. Rep. **59**: 522, 1944.
 Leibowitz, S., Kissin, M., and Rinzler, S. H.: Am. J. Med. **8**: 314, 1950.
 Lester, B. S., Denison, G. A., Posey, L. C., and Tate, G. M.: South. M. J. **35**: 325, 1942.
 Lorenz, G.: U. S. Nav. M. Bull. **42**: 560, 1944.
 Musser, J. H., and Bertucci, E. A., Jr.: Am. J. M. Sc. **209**: 86, 1945.
 Rosenbaum, H. D.: Arch. Int. Med. **78**: 531, 1946.
 Randall, R., and Cooper, H. K.: Science **100**: 133, 1944.
 Sacks, M. S.: Ann. Int. Med. **33**: 481, 1950.
 Senekjie, H. A.: J. A. M. A. **126**: 5, 1944.
 Sheldon, W. H.: Arch. Int. Med. **75**: 119, 1945.
 Stiles, W. W., and Sawyer, W. A.: J. A. M. A. **118**: 34, 1942.
 Stuart, R. D.: J. Path. & Bact. **58**: 343, 1946.
 Tievensky, G., and Schaeffer, B. G.: M. Ann. District of Columbia **13**: 11, 1944.
 Varadi, S.: Brit. M. J. **1**: 126, 1943.
 Weetch, R. S., and Colquhoun, J.: Lancet **1**: 906, 1949.
- Relapsing Fever*
- Ash, J. E., and Spitz, Sophie: Pathology of Tropical Diseases, Philadelphia and London, 1945, W. B. Saunders Co.
 Ashbel, R.: Ann. Trop. Med. **36**: 97, 1942.
 Bodman, R. L., and Stewart, I. S.: Brit. M. J. **1**: 291, 1948.
 Clarke, H. C.: Trop. Dis. Bull. **40**: 607, 1943.
 Chung, H. L.: Proc. Soc. Exper. Biol. & Med. **38**: 97, 1938.
 Cooper, E. L.: M. J. Australia **1**: 635, 1942.
 Davis, G. E.: U. S. P. H. Rep. **56**: 2464, 1941.
 Eads, R. B., Henderson, H. E., McGregor, T., and Irons, J. V.: Am. J. Trop. Med. **30**: 73, 1950.
- Findlay, G. M., Kirk, R., and Lewis, D. J.: Ann. Trop. Med. **35**: 149, 1941.
 Gillespie, J. O.: J. A. M. A. **104**: 1878, 1935.
 Greaves, F. C., Gezon, H. M., and Alston, W. F.: U. S. Nav. M. Bull. **43**: 1029, 1945.
 Heilman, F. R., and Herrell, W. E.: Proc. Staff Meet., Mayo Clin. **18**: 457, 1943.
 Huei-Lan Chung and Yu-Lin Wei: Am. J. Trop. Med. **18**: 661, 1938.
 Legerton, C. W., and Chambers, W. L.: U. S. Armed Forces M. J. **1**: 88, 1950.
 Lourie, E. M., and Collier, H. O. J.: Ann. Trop. Med. **37**: 200, 1943.
 Mazzotti, L.: Am. J. Hyg. **38**: 203, 1943.
 Novy, F. G., and Knapp, R. E.: J. Infect. Dis. **3**: 291, 1906.
 Ordman, D., and Jones, F. R.: South African M. J. **14**: 81, 1940.
 Reynolds, F. C.: California & West. Med. **47**: 170, 1937.
 Robinson, P.: Brit. M. J. **2**: 216, 1942.
 Selwyn-Clark, P. S., Le Fanu, G. H., and Ingram, A.: Ann. Trop. Med. **17**: 389, 1923.
 Stannus, H. S., and Bendit, M.: Lancet **1**: 103, 1942.
 Stein, G. J.: J. Exper. Med. **79**: 115, 1944.
 Strong, R. P.: M. Clin. North America **27**: 734, 1943.
 Taft, W. C., and Pike, J. B.: J. A. M. A. **129**: 1002, 1945.
 Varden, A. E.: Am. J. Dis. Child. **48**: 359, 1934.
 Wolff, B. P.: Ann. Int. Med. **24**: 203, 1946.
 Wynns, H. L., and Beck, M. D.: Am. J. Pub. Health **25**: 270, 1935.
- Sodoku*
- Bayne-Jones, S.: Internat. Clin. **3**: 235, 1931.
 Beeson, P. B.: J. A. M. A. **123**: 332, 1943.
 Brown, T. McP., and Nunemaker, J. C.: Bull. Johns Hopkins Hosp. **70**: 201, 1942.
 Burk, S. B., and Hodas, J. H.: Am. J. Surg. **60**: 453, 1943.
 Futaki, K., Takaki, F., Taniguchi, T., and Osumi, S.: J. Exper. Med. **23**: 249, 1916.
 Greenzard, J., and Hess, E. R.: J. A. M. A. **116**: 2393, 1941.
 Hitzig, W. M., and Lieberman, B. A.: Arch. Int. Med. **73**: 415, 1944.
 Ido, Y., Ito, H., Wanl, H., and Okuda, K.: J. Exper. Med. **26**: 377, 1917.
 Kaneko, R., and Kikuzo, O.: J. Exper. Med. **26**: 363, 1917.
 Leadingham, R. S.: Am. J. Clin. Path. **8**: 333, 1938.
 McDermott, E. N.: Quart. J. Med. **21**: 433, 1928.
 Ripley, H. S., and Van Sant, H. M.: J. A. M. A. **102**: 1917, 1934.
 Rogliano, A. G.: Surgery **11**: 632, 1942.
- Rat-Bite Fever and Haverhill Fever*
- Blake, F. G.: J. Exper. Med. **23**: 39, 1916.
 Blake, F. G., Horstmann, D. M., and Arnold, H.: Yale J. Biol. & Med. **16**: 589, 1944.
 Ferrell, E., Lordi, G. H., and Vogel, J.: Arch. Int. Med. **64**: 17, 1939.
 Levaditi, C., and Selbie, F. R.: Compte rend. Acad. d. sc. Paris **189**: 1332, 1929.
 Levaditi, C., Selbie, R. F., and Schoen, R.: Am. Inst. Pasteur **48**: 308, 1932.
 Parker, F., Jr., and Hudson, P. N.: Am. J. Path. **2**: 357, 1926.
 Place, E. H., Sutton, L. E., Jr., and Willner, O.: Boston M. & S. J. **194**: 285, 1926.
 Tunnicliff, R., and Meyer, K. M.: J. Infect. Dis. **23**: 555, 1918.
 Watkins, C. G.: J. Pediat. **28**: 429, 1946.
 Witzberger, C. M., and Cohen, H. G.: Arch. Pediat. **61**: 123, 1944.
- Fusospirochelosis*
- Benedek, T.: Surgery **11**: 75, 1942.
 Black, W. C.: J. Pediat. **20**: 145, 1942.
 Bowman, F. B.: Canad. M. A. J. **48**: 471, 1940.
 Corbus, B. C., and Harris, F. G.: J. A. M. A. **52**: 1474, 1909.
 Field, H., Jr.: J. Clin. Investigation **13**: 707, 1934.
 Greenblatt, R. B., and Wright, J. C.: Am. J. Syph., Gonor. & Ven. Dis. **20**: 654, 1936.
 Joseph, G. F.: South. M. J. **38**: 778, 1945.
 Kent, B. S.: Lancet **1**: 642, 1943.

- Kline, B. S., and Berger, S. S.: Arch. Int. Med. **56**: 753, 1935.
- Lichtenberg, H. H., Werner, M., and Lueck, E. V.: J. A. M. A. **100**: 707, 1933.
- Mac Gregor, A. B., and Long, D. A.: Brit. M. J. **2**: 686, 1944.
- Malter, H. L.: Mil. Surgeon **94**: 358, 1944.
- Manson, W. W.: J. A. M. A. **127**: 277, 1945.
- Mendelson, R. W.: J. A. M. A. **146**: 727, 1951.
- Pearce, W. F., and McDonald, J. B.: J. A. M. A. **128**: 342, 1945.
- Pund, E. R., Greenblatt, R. B., and Huie, G. B.: Am. J. Syph., Gonor. & Ven. Dis. **22**: 495, 1938.
- Schuessler, C. F., and Fairchild, J. M.: Bull. U. S. Army M. Dept. **85**: 15, 1945.
- Schwartz, B. M.: J. A. M. A. **128**: 704, 1945.
- Shallenberger, P. L., Denny, E. R., and Pyle, H. D.: J. A. M. A. **128**: 706, 1945.
- Smith, D. T.: Am. Rev. Tuberc. **16**: 584, 1927.
- Smith, D. T.: Oral Spirochetes and Related Organisms in Fusco-spirochetal Disease, Baltimore, 1933, Williams & Wilkins Co.
- Strieder, J. W., and Lynch, J. P.: New England J. Med. **234**: 1, 1946.
- Sweeney, J. S., Morginson, W. J., Robinson, R. W., and Kilpatrick, E. M.: J. Lab. & Clin. Med. **30**: 132, 1945.
- Tauber, E. B., and Goldman, L.: Arch. Dermat. & Syph. **34**: 630, 1936.
- Thomson, G. M.: Brit. M. J. **2**: 485, 1943.
- Tunnicliff, R.: J. Infect. Dis. **3**: 148, 1906.
- Tunnicliff, R.: J. Infect. Dis. **8**: 316, 1911.
- Turning, H. E., Szylejko, H. W., and Kern, R. A.: U. S. Nav. M. Bull. **45**: 479, 1945.
- von Haam, E.: Am. J. Trop. Med. **18**: 595, 1938.
- Weinstein, B. B.: Am. J. Obst. & Gynec. **45**: 136, 1943.
- Paggi, L. C., and Hull, E.: Ann. Int. Med. **20**: 686, 1944.
- Pariser, H., and Beerman, H.: Am. J. M. Sc. **208**: 547, 1944.
- Polayes, S. H., and Wickle, H. W.: Am. J. Surg. **71**: 406, 1946.
- Pund, E. R., and Auerbach, S. H.: Urol. & Cutan. Rev. **48**: 562, 1944.
- Pund, E. R., and Gotcher, V. A.: Surgery **3**: 34, 1938.
- Pund, E. R., and Greenblatt, R. B.: Arch. Path. **23**: 224, 1937.
- Pund, E. R., and Greenblatt, R. B.: J. A. M. A. **108**: 1401, 1937.
- Pund, E. R., Greenblatt, R. B., and Huie, G. B.: Am. J. Syph., Gonor. & Ven. Dis. **22**: 495, 1938.
- Pund, E. R., Huie, G. B., and Gotcher, V. A.: Am. J. Obst. & Gynec. **37**: 477, 1939.
- Pund, E. R., and McInnes, G. F.: Clinics **3**: 221, 1944.
- Pund, E. R., Smith, A. D., Hicks, D. Y., and Dienst, R. B.: South. M. J. **32**: 917, 1939.
- Reinstein, C. R., Dienst, R. B., and Greenblatt, R. B.: J. M. A. Georgia **37**: 452, 1948.
- Robertson, J. P., and Sharp, L.: Am. J. Surg. **34**: 322, 1936.
- Sheldon, W. H., Thebaut, B. R., Heyman, A., and Wall, M. J.: Am. J. M. Sc. **210**: 237, 1945.
- Sobel, N., and Pensky, N.: Arch. Dermat. & Syph. **48**: 494, 1943.
- Symmers, D., and Frost, A. D.: J. A. M. A. **74**: 1304, 1920.
- Torpil, R., Greenblatt, R. B., and Pund, E. R.: Am. J. Surg. **44**: 551, 1939.

Lymphogranuloma Venereum

- Bacon, H. E., and Griffin, O. P.: Am. J. Surg. **56**: 166, 1942.
- Beeson, P. B., and Miller, E. S.: Am. J. Pub. Health **34**: 1076, 1944.
- Bloom, D.: New York State J. Med. **38**: 616, 1938.
- Brinkley, G. E., and Derrick, W. A.: Am. J. Digest. Dis. **12**: 46, 1945.
- Cardwell, E. S., Jr., and Pund, E. R.: J. M. A. Georgia **29**: 60, 1940.
- Cole, H. N.: J. A. M. A. **101**: 1069, 1933.
- Costello, M. J., and Cohen, J. A.: Arch. Dermat. & Syph. **44**: 391, 1941.
- Coutts, W. E.: J. Urol. **49**: 595, 1943.
- Coutts, W. E., Opaxo, L., and Montenegro, L.: Am. J. Digest. Dis. **7**: 287, 1940.
- D'Aunoy, R., and von Haam, E.: Arch. Path. **27**: 1032, 1939.
- D'Aunoy, R., von Haam, E., and Lichtenstein, L.: Am. J. Path. **11**: 737, 1935.
- D'Aunoy, R., and Schenken, J. R.: J. A. M. A. **110**: 799, 1938.
- David, V. C., and Loring, M.: J. A. M. A. **106**: 1875, 1936.
- Editorial: Ann. Int. Med. **22**: 891, 1945.
- Frei, W.: J. A. M. A. **110**: 1653, 1938.
- Frei, W.: Arch. Dermat. & Syph. **47**: 830, 1943.
- Grace, A. W.: J. A. M. A. **122**: 74, 1943.
- Grace, A. W., Rake, G., and Shaffer, M. F.: Proc. Soc. Exper. Biol. & Med. **45**: 259, 1940.
- Grace, A. W., and Suskind, F. H.: Am. J. Path. **16**: 169, 1940.
- Gray, L. A.: Surg., Gynec. & Obst. **62**: 745, 1936.
- Gray, S. H., Hunt, G. A., Wheeler, P., and Blache, J. O.: J. A. M. A. **106**: 919, 1936.
- Greenblatt, R. B.: Am. J. Surg. **49**: 411, 1940.
- Greenblatt, R. B.: U. S. P. H. Service, Supp. No. 19, 1943.
- Hansmann, G. H.: Surg. Gynec. & Obst. **39**: 72, 1924.
- Hellerström, S.: Acta. dermat.-venereol. Supp. I, 1929.
- Hellerström, S., and Wassen, E.: Swedish College of Physicians, Lennander Lecture, May 22, 1933.
- Jones, C. A., and Rome, H. P.: Internat. Clin. **2**: 178, 1938.
- Kampmeier, R. H., and Larsen, R. M.: Am. J. Syph., Gonor. & Ven. Dis. **26**: 316, 1942.
- Koteen, H.: Medicine **24**: 1, 1945.
- Law, W. L.: Lancet **1**: 300, 1943.
- Levy, H.: Arch. Pediat. **57**: 441, 1940.
- Levy, J. G., Holder, F. C., and Bullowa, J. G. M.: Am. J. Digest. Dis. **9**: 237, 1942.
- Anderson, K., De Monbreun, W. A., and Goodpasture, E. W.: Am. J. Syph., Gonor. & Ven. Dis. **29**: 165, 1945.
- Anderson, K., De Monbreun, W. A., and Goodpasture, E. W.: J. Exper. Med. **81**: 25, 1945.
- Anderson, K., Goodpasture, E. W., and De Monbreun, W. A.: J. Exper. Med. **81**: 41, 1945.
- D'Apoll, R., and von Hamm, E.: Am. J. Path. **14**: 39, 1938.
- Dulaney, A. D., Guo, K., and Packer, H.: J. Immunol. **59**: 335, 1948.
- Greenblatt, R. B.: Supp. No. 19 Ven. Dis. Inform., 1943.
- Greenblatt, R. B., Dienst, R. B., Pund, E. R., and Torpin, R.: J. A. M. A. **113**: 1109, 1939.
- Greenblatt, R. B., Torpin, R., and Pund, E. R.: Arch. Dermat. & Syph. **38**: 358, 1938.
- Hanna, C. B., and Pratt-Thomas, H. R.: South. M. J. **41**: 776, 1948.
- Lipp, R. G., and Bibby, D. E.: West. J. Surg. **58**: 173, 1950.
- Lyford, J. B., III, Scott, R. B., and Johnson, R. W., Jr.: Am. J. Syph., Gonor. & Ven. Dis. **28**: 588, 1944.
- Margolis, G.: Am. J. Path. **21**: 543, 1945.
- Packer, H., Turner, H. B., and Dulaney, A. D.: J. A. M. A. **136**: 327, 1948.

- Lichtenstein, L.: Am. J. Surg. 31: 111, 1936.
Lichtenstein, L.: Ann. Surg. 104: 279, 1936.
Luger, N. M.: New England J. Med. 238: 44, 1948.
Mathewson, J. C.: J. A. M. A. 110: 709, 1938.
McKee, C. M., Rake, G., and Shaffer, M. F.: Proc. Soc. Exper. Biol. & Med. 44: 410, 1940.
Palmer, W. L., Kirsner, J. B., and Rodaneche, E. C.: J. A. M. A. 118: 517, 1942.
Pund, E. R., and Dick, F., Jr.: Urol. & Cutan. Rev. 51: 345, 1947.
Pund, E. R., Greenblatt, R. B., and Huie, G. B.: Am. J. Syph., Gonor. & Ven. Dis. 22: 495, 1938.
Pund, E. R., and Lacy, G. R., Jr.: Am. Surgeon 17: 711, 1951.
Rake, G., and Jones, H. P.: J. Exper. Med. 75: 323, 1942.
Rake, G., McKie, C. M., and Shaffer, M. F.: Proc. Soc. Exper. Biol. & Med. 43: 332, 1940.
Reichle, H. S., and Connor, W. H.: Arch. Dermat. & Syph. 32: 196, 1935.
Root, H. S.: Canad. M. A. J. 47: 246, 1942.
Sabin, A. B., and Aring, C. D.: J. A. M. A. 120: 1376, 1942.
Shaffer, M. J., Rake, G., and Grace, A. W.: Am. J. Syph., Gonor. & Ven. Dis. 26: 271, 1942.
Sheldon, W. H., Wall, M. J., Slade, J. DeR., and Heyman, A.: Arch. Int. Med. 82: 410, 1948.
Smith, E. B., and Custer, R. P.: J. Urol. 63: 546, 1950.
Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: Am. J. M. Sc. 197: 575, 1939.
Tauber, R.: Ann. Surg. 122: 111, 1945.
Thompson, R. G., and Higgins, E. L.: Am. J. Syph., Gonor. & Ven. Dis. 33: 473, 1949.
Torpin, R., Greenblatt, R. B., Pund, E. R., and Sanderson, E. S.: Am. J. Surg. 43: 688, 1939.
von Haam, E., and D'Aunoy, R.: J. A. M. A. 106: 1642, 1936.
Wien, M. S., Perlstein, M. O., and Neiman, B. H.: Arch. Path. 19: 331, 1935.
Wood, W. H., Jr., and Felson, H.: Ann. Int. Med. 24: 904, 1936.
Wright, L. T., and Logan, M.: Arch. Surg. 39: 108, 1939.
Zarafonetis, J. D.: New England J. Med. 230: 567, 1944.

Chapter 14

RICKETTSIAL AND VIRAL DISEASES

HENRY PINKERTON

In order to understand the changes produced in tissues by rickettsiae and viruses, it is essential to have a clear concept of their biologic characteristics.¹⁻⁶ These two groups of infective agents are obligate intracellular parasites which live and multiply within tissue cells by diverting the metabolic mechanisms of these cells to their own use. A given rickettsia or virus will therefore cause disease in an animal only if it gains entrance to cells in which the metabolites necessary for its growth are available. Thus the metabolic peculiarities of cells, which depend on genes, enzymes, hormones, and vitamins, determine their susceptibility to rickettsial and viral infections. The effects of vitamin deficiencies on diseases caused by intracellular parasites are discussed in Chapter 17.

Interrelationships of Bacteria, Rickettsiae, and Viruses

Infective agents vary greatly in their ability to live independently. Nearly all pathogenic bacteria contain enzyme systems which enable them to grow on relatively simple cell-free bacteriologic media. In infected tissues, such organisms multiply extracellularly in the body fluids. They are rarely seen within cells except when engulfed by phagocytic cells, in which they are usually destroyed. Facultative intracellular parasites, such as *Pasteurella tularensis* and *Bartonella bacilliformis*, multiply extensively within cells, but grow also in intracellular fluids under certain conditions. These organisms require partially predigested food, and are cultivated in cell-free media with difficulty.

The obligate intracellular parasites include primarily the rickettsiae and viruses, although certain protozoa, fungi, and bacteria (*Mycobacterium leprae*, for example) also belong to this group. The metabolites necessary for the growth of these agents are unstable compounds which are formed by intracellular enzymes as intermediary metabolic products, and which are appropriated by the parasites for their own use. These agents cannot be cultivated in cell-free media, but only in media containing living or surviving cells. In the laboratory, they are propagated in living animals, in tissue cultures, in chick embryos, or in the cells lining the membranes of the developing chick embryo. The latter are peculiarly

susceptible to infection in spite of the fact that the hatched chicken is usually completely resistant.

Bacteria, rickettsiae, and viruses, cannot be considered as sharply separated groups. They may be arranged in a series with progressive loss of independent metabolic activity, and increasing metabolic dependence on the enzyme systems of their host cells. In general, also, there is progressive diminution in size. The rickettsiae and the "elementary bodies" of some of the larger viruses are smaller than most bacteria, and are on the border line of visibility with the ordinary microscope (0.30 to 0.25 micron in least diameter) while smaller viruses range from 0.25 to 0.008 micron in least diameter and can be resolved only with the electron microscope. Bacteria and rickettsiae, with few exceptions, are too large to pass through unglazed porcelain filters, while viruses readily pass such filters.

Pathologic Lesions Produced by Rickettsiae and Viruses

The lesions produced by rickettsiae and viruses have many features in common, and differ in many respects from lesions caused by free-living bacteria. Cutaneous eruptions are common in rickettsial and viral infections. In the brain, where bacteria characteristically cause localized abscesses or purulent meningitis, rickettsiae and viruses cause diffuse nonsuppurative encephalitis. Similarly in the lung, where bacteria cause purulent exudation in the alveoli and bronchioles, on the pleural surfaces, or in localized abscesses, rickettsiae and viruses cause diffuse inflammation of the alveolar and bronchiolar walls (interstitial pneumonia). This tendency to cause diffuse or interstitial inflammation is the result of the growth of these agents in cells of one type, as the ganglion cells of the brain (poliomyelitis) or vascular endothelium (typhus rickettsiae).

RICKETTSIAL DISEASES

The name *Rickettsia prowazekii* was applied by da Rocha-Lima⁷ in 1916 to the etiological agent of typhus fever in recognition of the pioneer work of Ricketts and von Prowazek on typhus and Rocky Mountain spotted fever. It soon be-

came clear that a large number of minute organisms resembling bacteria morphologically could be found within the cells of the tissues of many species of arthropods, and it became customary to call these organisms rickettsiae. The majority of these organisms are not pathogenic either for the arthropods in which they live or for mammals. A few of them, however, because of their peculiar ability to invade mammalian cells, cause important diseases of man and other mammals.

Rickettsial diseases in different parts of the world have been given a large number of different names. The clinical pictures show considerable variation, partly as a result of varia-

Q fever stands apart from the other rickettsial diseases, the picture being primarily one of pulmonary involvement. In general, epidemic typhus and most strains of Rocky Mountain spotted fever and of tsutsugamushi disease have a high mortality. Recently discovered chemotherapeutic agents (chloramphenicol, aureomycin, and terramycin) have, however, greatly reduced the mortality from all rickettsial diseases.⁸

TABLE IV
RICKETTSIAL DISEASES OF MAN

DISEASES	ETOIOLOGICAL AGENTS	VECTORS	DISTRIBUTION
A. Typhus group			
1. Epidemic	<i>R. prowazekii</i>	Lice	Europe, Asia, Africa, Central and South America
2. Murine	<i>R. mooseri</i>	Rat fleas	World-wide
B. Spotted fever group			
1. "Rocky Mountain" spotted fever	<i>Dermacentroxyenus rickettsii</i> (<i>R. rickettsii</i>)	Ticks	United States, Canada, Central and South America
2. Boutonneuse fever	<i>R. conorii</i>	Ticks	Mediterranean area
3. South African tick-bite fever	<i>R. pipiperi</i>	Ticks	South Africa
4. Rickettsialpox	<i>R. akari</i>	Mites	New York City
C. Tsutsugamushi disease	<i>R. tsutsugamushi</i>	Mites	Western Pacific Islands, Indo-China, Burma, India
D. Q fever	<i>R. burneti</i> (<i>R. diaporica</i>)	Ticks?	Australia, United States, Panama, Mediterranean area
E. Trench fever	<i>R. pediculi</i>	Lice	Europe

tions in virulence, and partly from strain modifications caused by residence in different arthropod vectors and intermediate mammalian hosts. Thorough morphological, clinical, and immunological studies have shown, however, that all known human rickettsial diseases fall into one or another of the five groups shown in Table IV. All of these groups are immunologically distinct.

Clinically, typhus, spotted fever, and tsutsugamushi disease are acute febrile infections, with cutaneous eruption and evidence of involvement of the central nervous system. Clinical differentiation between these three groups is based on minor differences, and may be difficult in atypical sporadic cases. A rash occurs also in trench fever, but this disease runs a milder course and is characterized by pain and tenderness in muscles, bones, and joints, and by its recurrent nature.

The Typhus Group

Two varieties of typhus fever are recognized: the louse-borne (epidemic or human) type, and the rat flea-borne (endemic or murine) type. Louse-borne typhus has been responsible for devastating epidemics in historical times. In the major epidemic which occurred during and shortly after the World War of 1914-1918, it is estimated that some fifteen million cases occurred, with over three million deaths. This epidemic occurred in spite of the fact that Nicolle⁹ proved the louse transmission of the disease in 1909. Eventual control of the epidemic, however, was due largely to delousing of large groups of the civilian population.¹⁰ During World War II, epidemics which threatened to be severe broke out in several areas but, in most cases, were rapidly brought under control.¹¹ Improved methods of delousing and prophylactic vaccination probably prevented a recurrence of the tragedy of World War I.

Murine typhus, with a reservoir in wild rats, is a disease of almost world-wide distribution. Although Brill¹² in 1898 and in 1910 called

attention to small outbreaks of typhus in New York, these were believed to represent importation of the disease from Europe. It was not until the studies of Maxey¹³ in 1926 and of Dyer, Rumreich, and Badger¹⁴ in 1931 that the presence of typhus in rats and its transmission to man by rat fleas became established. Murine

typhus clinically is somewhat milder than louse-borne typhus. By means of complement fixation and rickettsial agglutination tests, the two varieties may be differentiated from one another.¹⁵ Under conditions of crowding, starvation, and louse infestation, it is assumed, without conclusive proof, that murine typhus

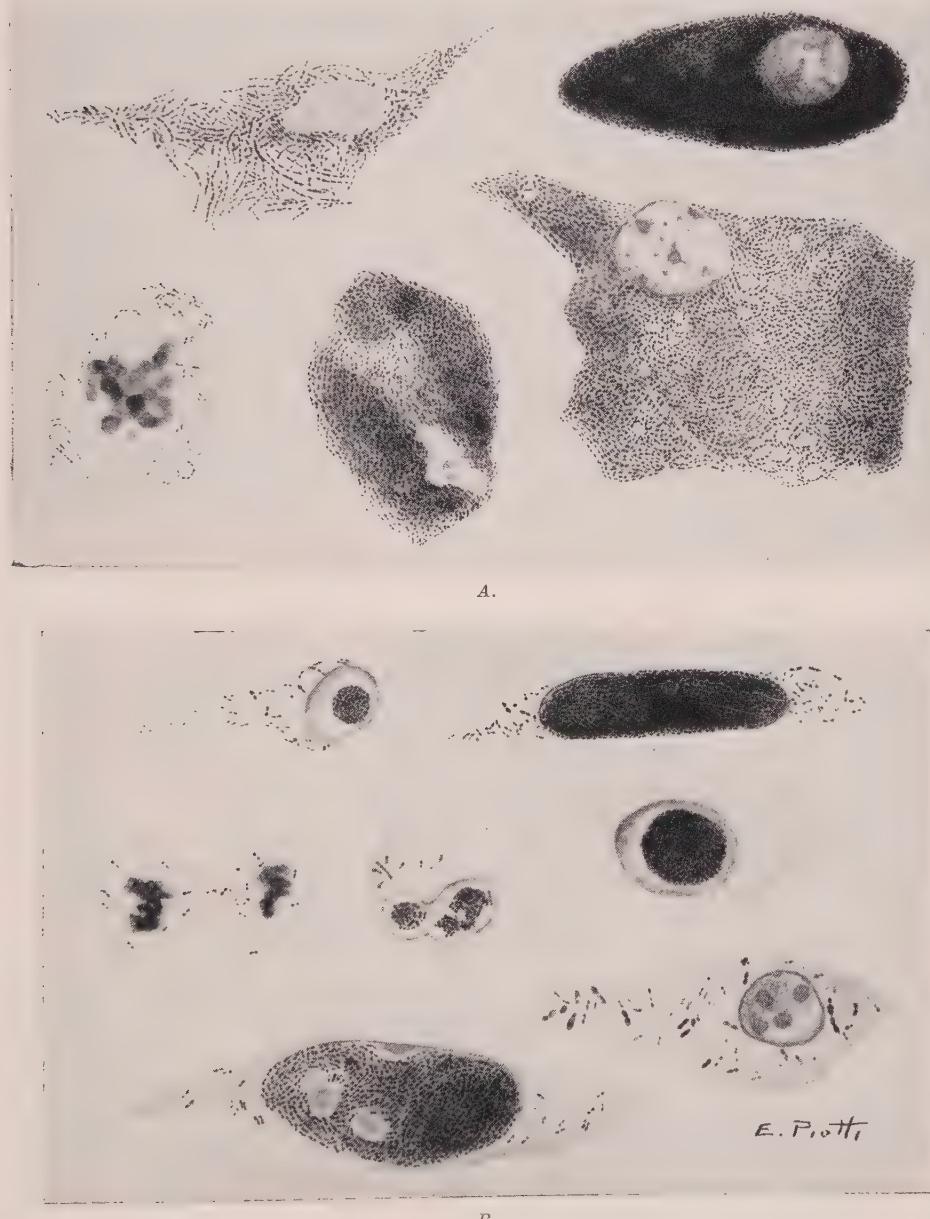


Fig. 197.—Comparison of intracellular growth patterns of typhus and spotted fever rickettsiae in tissue culture.

A, Typhus rickettsiae grow massively in the cytoplasm, but do not invade nuclei. One cell is in mitosis.

B, Spotted fever rickettsiae grow most freely in nuclei, some of the nuclear clusters resembling viral inclusions. Note the behavior in the cell dividing mitotically.
(From Berkovitz, Clinical Tropical Medicine, Paul B. Hoeber, Inc.)

may be transformed into the more severe epidemic or human type.

The etiological agents of the two types of typhus, *Rickettsia prowazekii* and *R. mooseri* are morphologically identical. They are minute diplobacilli, each unit of the diploid form averaging about 0.6 by 0.3 micron. (See Fig. 197.) Chain formation is occasionally seen. The organisms as seen in tissues are always intracellular, since rapid lysis occurs if they are set free from degenerating cells. Giemsa staining after Regaud's fixation is the best method for staining the organism in tissues.

Pathologic Lesions.—Typhus rickettsiae multiply in the intestinal lining cells of the louse and flea, and are passed in the feces of these arthropods. They enter human skin through the puncture wound made by the bite of the louse or flea, and multiply slowly for several days in vascular endothelium of the capillaries in the corium. A grossly visible local lesion is not produced in the skin.

Eventually entering the blood stream, organisms are carried in small numbers to the capillary bed in all parts of the body, where they undergo extensive multiplication, particularly in the endothelial cells lining the capillaries of the brain, skin, and heart. Minute capillaries are occluded by the swelling and proliferation of endothelial cells, and larger vessels less often by the formation of fibrin thrombi.¹⁶

Since the lesions involve mainly the blood vessels of microscopic size, gross lesions are not conspicuous. In fatal cases the spleen is usually considerably enlarged, and there is cloudy swelling of the viscera. The petechial hemorrhagic lesions of the late stage of the cutaneous eruption may remain visible after death. Occasionally one or two gross areas of cutaneous necrosis may be seen as a result of occlusion of larger vessels.

Perivascular accumulations of mononuclear cells, the so-called typhus nodules, are the most characteristic microscopic feature of the disease. These nodules may be in close association with obviously damaged capillaries or may represent the end result of complete occlusion and disintegration of small capillaries. These microscopic lesions are most numerous in the skin, brain, and cord but may be found in almost any organ on careful search. The focal lesions in the central nervous system (Fig. 198) are most important for histologic diagnosis. Neurog-

lia cells are the most prominent component of these lesions, but occasional macrophages, plasma cells, and neutrophiles may be seen. Perivascular "cuffing" and petechial hemorrhages are usually present. Except for the more conspicuous involvement of vascular endothelium and the absence of evidence of primary neuronal damage, these lesions resemble those seen in various types of viral encephalitis (see page 315).

In the heart, in addition to the focal lesions, a diffuse infiltration of mononuclear cells is seen between the myocardial fibers (Fig. 199), and occasional necrotic fibers are seen.

Bronchopneumonia of bacterial origin is a common complication in fatal cases. Mild interstitial pneumonitis is occasionally seen, but this lesion is much less conspicuous than that seen in tsutsugamushi disease and in Q fever.

In the kidney, perivascular and diffuse mononuclear cell infiltration is usually seen in variable degree. There is also some vacuolization of tubular epithelium, and an early acute diffuse glomerulonephritis, manifested by endothelial hyperplasia and fusion of capillary loops.¹⁸ These renal changes probably are of toxic origin, and are similar to the lesions seen in many other infectious diseases.

The liver shows periportal mononuclear cell infiltration, a variable degree of fatty change, and occasionally small foci of necrosis of liver cells with the accumulation of mononuclear phagocytes. The hepatic changes are not strikingly different from those seen in a number of acute infections.

A soluble antigen is set free from typhus rickettsiae in the process of disintegration.¹⁷ This has been shown by electron microscope study to consist of submicroscopic particles of capsular substance. Rickettsial toxins are unstable, and disappear with the complete disintegration of the organisms. These toxins are fatal when injected into mice, and may be responsible for certain lesions in man, particularly myocarditis and nephritis, but information on this point is lacking. It has been suggested that allergic reactions to toxins may be important in the pathogenesis of rickettsial lesions.¹⁸ With suitable technique, rickettsiae may be demonstrated in the endothelium of

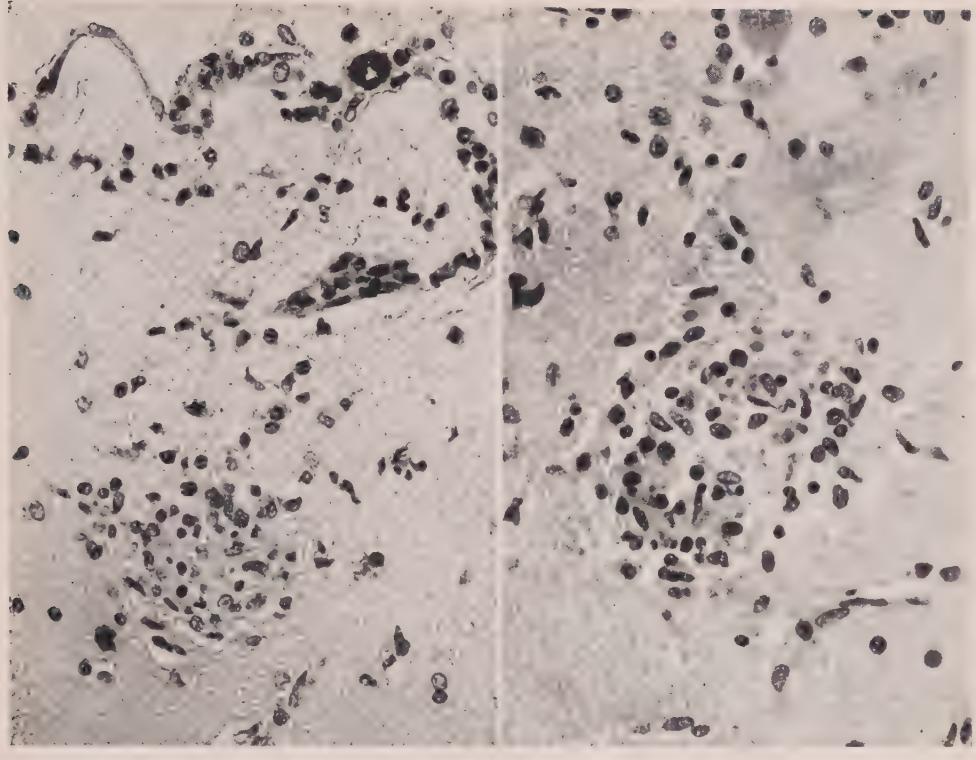


Fig. 198.—“Typhus nodules” of brain are frequent in gray matter (A). They are generally considered to be in relation to a blood vessel although the vessel may not always be visible. The histologic components of these proliferative foci are predominantly neuroglia cells with a few leukocytes and plasma cells (B). (AFIP Nos. 77543 and 78556. From Ash and Spitz. Pathology of Tropical Diseases, W. B. Saunders Co.)

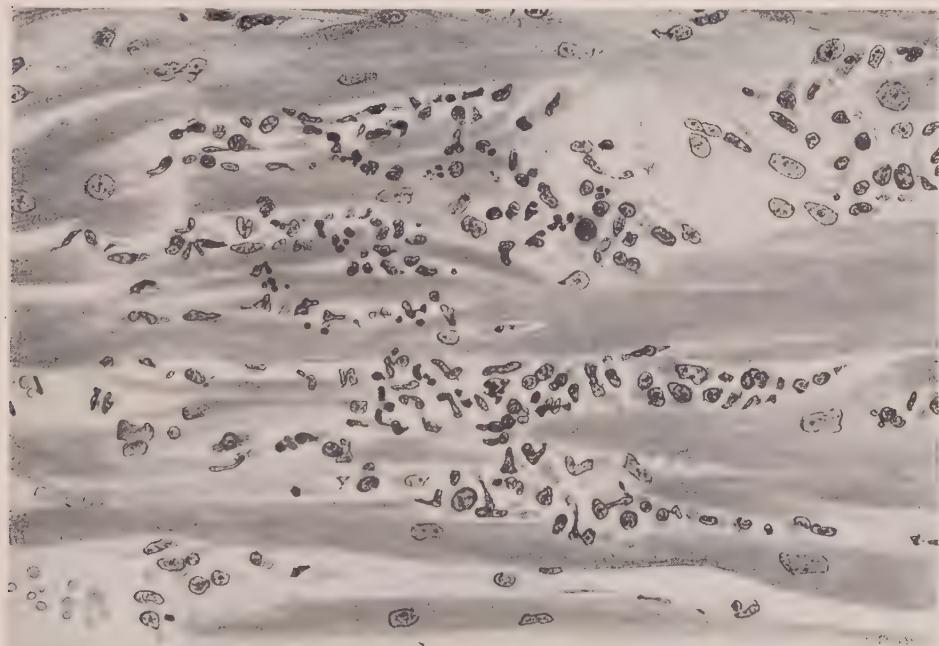


Fig. 199.—Myocarditis in typhus fever. There is infiltration of mononuclear cells and neutrophiles between the muscle fibers and a minute area of necrosis in the myocardial fibers. (From Wolbach, Palfrey, and Todd, The Etiology and Pathology of Typhus, Harvard University Press.)

damaged capillaries in the skin and, with great difficulty, in the brain and in other organs. Extracellular rickettsiae are not seen.

Clinical Pathologic Correlation.—Typhus fever is characterized clinically by sudden onset with severe headache, mild chills, and fever. The fever reaches its height at the end of the first week, terminating by rapid lysis, in uncomplicated cases, on the fourteenth to sixteenth days. The rash, which appears between the fourth and eighth days of illness, is at first macular and later becomes hemorrhagic as a result of capillary occlusion.

The neurological manifestations, including delirium, stupor, and coma in unfavorable cases, are clearly explainable by the cerebral changes. Death may be caused by the encephalitis, by the myocarditis, by secondary bacterial pneumonia, or by general toxemia. Sudden death from myocardial failure may occur without the usual evidence of cardiac decompensation. There is also evidence that a shocklike condition, with low blood pressure, hemoconcentration, and peripheral circulatory failure may be a cause of death in many cases.¹⁹ Impairment of renal function has also been stressed,²⁰ and correction of these physiological disturbances, controlled by frequent chemical studies of the blood, may be indicated in patients who are critically ill.

The Spotted Fever Group

Rocky Mountain spotted fever, Eastern spotted fever, and São Paulo "typhus" (Brazilian spotted fever) are essentially identical, even though different species of ticks are involved in their transmission.²¹ Boutonneuse fever, in which the dog is the intermediate host, is characterized by low mortality, a local ulcer (*tache noire*) at the site of attachment of the tick, and certain constant immunologic differences from the three strains mentioned above. Although complete cross-immunity may be demonstrated in guinea pigs between boutonneuse fever and Rocky Mountain spotted fever, cross-vaccination and complement fixation tests serve to differentiate them.²² South African tick-bite fever and rickettsialpox also appear to be separate entities, although obviously belonging in the spotted fever group.

The etiological agent of Rocky Mountain spotted fever, *Dermacentro xenus rickettsi*, shows slight differences morphologically from *Rickettsia prowazekii*.²³ Unlike the latter organism, it is present in the salivary glands of its arthropod vector, the tick, and is actually injected into the skin at the time of feeding on its mammalian host. It is transmitted in ticks from generation

to generation by infection of the ova. In ticks and in tissue cultures, rarely in mammals, spotted fever rickettsiae form compact clusters within the nuclei of infected cells (Fig. 197), somewhat resembling the nuclear inclusions of viral diseases. *D. rickettsi* has a more generalized cytological distribution than *R. prowazekii*, growing in nearly all types of tissue in the tick, and in man invading smooth muscle cells of the arteriolar walls as well as vascular endothelium.

Pathologic Lesions.—The lesions in spotted fever so closely resemble those of typhus that it is simpler to point out the differences than to enumerate them completely. The deeper invasion of arteriolar walls causes more extensive thrombotic vascular occlusion (Fig. 200). This is reflected in the more hemorrhagic character of the rash and in more frequent cutaneous necrosis, involving especially the scrotum, fingers, toes, elbows, and ears. In the brain, somewhat larger vessels are more often involved, and focal areas of demyelinization (microinfarcts) are added to the other lesions previously described as characteristic of typhus.²⁵ In contrast to typhus, the white matter is commonly involved. The spleen is larger in spotted fever than in typhus, and is usually palpable. The myocardial and pulmonary lesions are comparable to those of typhus fever. The pathologic physiology and mechanisms of death are also similar.

Clinically there is also striking similarity in the two diseases. Differential features are the earlier appearance of the rash in spotted fever (two to five days after the onset of fever), its more hemorrhagic and frequently confluent petechial character, and its appearance first on the extremities, with involvement of the palms and soles. The mortality, before the advent of chemotherapy, varied from 1 to 95 per cent, being consistently high in certain localities.

Rickettsialpox.—This type of rickettsial infection was first described²⁶ in New York City in 1946. Clinically there is an initial cutaneous lesion, at first papular but later becoming vesicular and eventually developing into a black eschar 1 to 1.5 cm. in diameter. Several days after the appearance of the initial lesion, there is a rise in temperature, and a generalized maculopapular eruption which soon becomes vesicular, so that the lesions resemble those of chickenpox.

Infection is transmitted by a rodent mite (*Allodermanyssus sanguineous*) and the etiological agent, *Rickettsia akari* has been recovered from this mite as well as from one of its common hosts,

the house mouse. This organism is antigenically related to *D. rickettsii*, but shows certain individual characteristics. Like other members of the spotted fever group it grows within nuclei of infected cells in the embryonated egg.

Little is known of the systemic pathology of the disease in man, since it appears to have no mortality. The local lesion shows only non-specific inflammation and necrosis. The generalized cutaneous lesion shows vascular endothelial proliferation, with perivascular accumulations of mononuclear cells. The pathological changes in guinea pigs include scrotal redness and swelling and inflammation of the tunica vaginalis comparable to that seen with mild strains of spotted fever.

for more than a century, while acceptable proof of arthropod transmission has been presented only in recent years.

In World War II, tsutsugamushi disease assumed great military importance, and was studied carefully by American and Australian investigators, who readily transmitted it to mice by the intraperitoneal injection of blood from human cases.²⁷

The etiological agent, *Rickettsia tsutsugamushi*, is morphologically similar to *R. prowazekii* and *D. rickettsii*. It is transmitted by the bites of the larval forms of several species of tropical mites belonging to the genus *Trombicula*, but par-

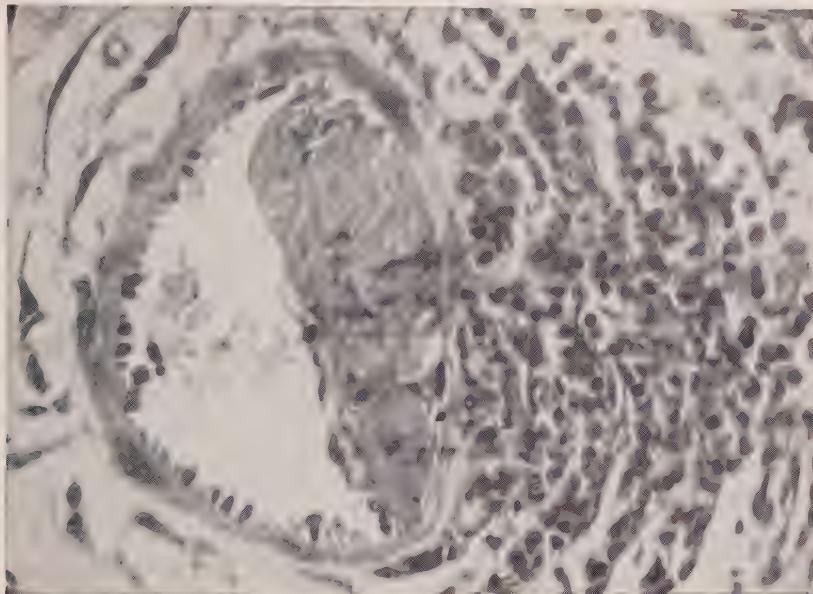


Fig. 200.—Spotted fever, showing the characteristic vascular pathology. A fibrin thrombus partially occludes the lumen of the vessel, and there is a focal perivascular collection of lymphocytes and macrophages. (From Anderson, Synopsis of Pathology, The C. V. Mosby Co.)

The Tsutsugamushi Group

Rickettsial diseases of the tsutsugamushi group occur in Japan, China, Indo-China, Sumatra, Australia, New Guinea, and several other islands and countries near the western Pacific Coast. Various other names have been applied to strains of this disease, including "mite typhus," "scrub typhus," "tropical typhus," etc. Different strains have not been studied extensively from a comparative point of view, and the possible occurrence of significant varieties, comparable to the murine and human varieties of typhus, has not been fully excluded. It is of interest that the Japanese name, tsutsugamushi (disease insect), has been in use

ticularly by *T. akamushi*. Voles, mice, and probably other rodents act as intermediate mammalian hosts. Credit for establishing the rickettsial nature of the disease belongs to a number of Japanese investigators, notably Hyashi, Nagayo, Ogata, Kawamura, and their collaborators, who propagated the organism by serial injection into the testicle of the rabbit²⁸ and into the anterior chamber of the rabbit's eye.²⁹ It has been cultivated in the cells lining the yolk sac of the fertile egg.

Clinically, tsutsugamushi disease resembles typhus and spotted fever. A distinctive feature, which, however, is not always present, is a localized area of cutaneous necrosis and ulceration at the site of attachment of the larval mite, with swelling and inflammation of the regional lymph nodes. In strains associated with this local lesion, the mortality, without chemotherapy, is high (20 to 60 per cent) while in the absence of the local lesion it is considerably lower. The appearance of the local lesion several days be-

fore the onset of fever permits early and effective chemotherapeutic treatment. The rash involves the palms and soles, but rarely becomes hemorrhagic, resembling that of measles. Neurological symptoms resemble those seen in typhus and spotted fever.

The pathologic lesions also resemble those of typhus and spotted fever.¹⁸ The tendency for capillary thrombosis to occur is less than in typhus and markedly less than in spotted fever. This fact explains the nonhemorrhagic character of the rash. Sections of the local lesion (eschar) show ulceration and necrosis of the epidermis, and large collections of neutrophiles and mononuclear cells in the underlying tissue.

Rickettsiae may be found in Giemsa-stained film preparations from these serosal exudates, but it is very difficult to demonstrate organisms in paraffin sections of infected tissues.

Q Fever

This disease was first described by Derrick,³⁰ in 1937, chiefly among slaughterhouse workers and dairy farmers. Burnet and Freeman subsequently described a rickettsia-like organism in smears from the spleen of infected mice. This organism was named *Rickettsia burneti* by Derrick. Meanwhile, Davis and Cox recovered

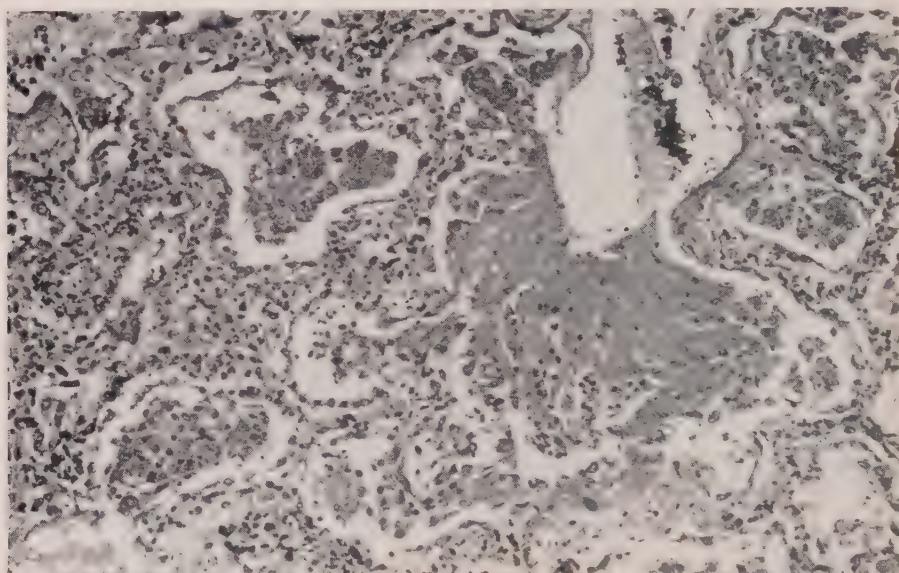


Fig. 201.—Interstitial pneumonitis in tsutsugamushi disease showing (1) septal edema and mononuclear cell infiltration, (2) macrophages and partially organized alveolar exudate, (3) prominent alveolar lining. (AFIP No. 82718. From Ash and Spitz, Pathology of Tropical Diseases, W. B. Saunders Co.)

The lesion often is pustular, with a black necrotic center. The lymph nodes draining the local ulcer show acute and chronic lymphadenitis. Occasionally two or more eschars are seen. Generalized vascular lesions, encephalitis, myocarditis, and renal lesions are similar to those in typhus and spotted fever. Primary interstitial pneumonitis is more conspicuous than in typhus and spotted fever. (Fig. 201.) Involvement of serous surfaces, in the form of mild rickettsial peritonitis, pleuritis, and pericarditis with collection of small amounts of serous fluid, is a unique feature of tsutsugamushi disease.

an organism from ticks in Montana which they named *Rickettsia diaporica*. This organism was found to be pathogenic for guinea pigs, and a case of laboratory infection was reported by Dyer in 1938. In 1940, an institutional outbreak occurred in Washington, D. C.

Present evidence indicates that *Rickettsia burneti* and *R. diaporica* are essentially identical³¹ and it is assumed that Australian Q fever and American Q fever are one and the same disease, since the clinical features of the disease are the same in both countries. Evidence that the disease may be widespread geographi-

cally and of common occurrence has been presented recently.³² Certain epidemics of atypical pneumonia have been shown to be caused by *R. burnetii* (see page 326).

Rickettsia burnetii (diaporica) is a facultative intracellular parasite, growing both intracellularly and extracellularly in infected tissues. It is readily cultivated in the yolk sac of the fertile egg,³³ but has resisted all attempts to grow it in cell-free media. It resembles the other rickettsiae described, but appears slightly larger in stained preparations. In spite of this fact, the organisms pass through porcelain filters which apparently do not allow typhus rickettsiae to pass. The organisms are often present in very large numbers in tissues of infected guinea pigs. They are transmitted from generation to generation in ticks by infection of the ova. The intracellular forms tend to occur in compact clusters in the cytoplasm, simulating the picture seen in cells infected with *Bartonella bacilliformis*. For some unknown reason, organisms have not been demonstrated satisfactorily in human tissues, although injection of guinea pigs with infected lung tissue or blood from human cases often causes peritonitis with numerous visible organisms.

The epidemiology of the disease is not yet clear. Although the assumption has been made that the disease may be transferred by droplet infection, recent evidence does not favor this concept. *R. burnetii* apparently multiplies in the mammary glands of latently infected cows, and may be recovered from milk, suggesting strongly a situation parallel to that obtaining in brucellosis. There is also evidence that infection occasionally may be acquired by the bite of a tick. Laboratory infection from strains isolated in experimental animals are said to be very common.

Clinically, Q fever differs markedly from other rickettsial diseases. It is an acute febrile illness, usually without cutaneous eruption, and with inconspicuous mental symptoms. The outstanding manifestations are in the respiratory system. Respirations may be normal or somewhat increased, and there is usually a persistent dry cough. X-ray examination reveals atypical bronchopneumonia, often of a degree not suspected from the clinical picture. The duration of the disease varies from five or six days in mild cases, up to twenty-five days or more in the more severe cases. The mortality is low. A complement fixation test which has been developed recently is of great value as a method of case finding and has been used in the investigation of epidemics of atypical pneumonia.³²

The pathologic lesions are most prominent in the lungs. Grossly there is patchy, firm, granular consolidation. Microscopically the picture is that of interstitial pneumonitis, with mononuclear infiltration of the alveolar walls and some rounding up of the alveolar lining cells. The alveoli contain a serofibrinous exudate in which only a few cells, chiefly mononuclear cells, are present. The picture resembles that

of a viral pneumonia, such as that seen in psittacosis. The involvement is more severe than that usually seen in typhus, spotted fever, and tsutsugamushi disease. Changes in the other organs are not striking.

Trench Fever

Trench fever was first recognized in 1915, when it became a serious cause of disability among troops. It was extensively studied at that time, and the louse transmission of the disease was established beyond question.³³ A few small outbreaks were reported in World War II, but little has been added to our knowledge of the disease.

Etiology.—The disease may be transmitted experimentally from person to person by louse feeding or by rubbing feces from infected lice into the scarified skin. The blood of recovered patients remains infective for lice over a period of months or even years.

It has been shown repeatedly that lice which have no microorganisms in their intestinal tracts show large numbers of small bacillary bodies there after feeding on trench fever patients. These organisms are extracellular, and in this respect are not typical rickettsiae. The problem is complicated by the fact that apparently normal lice at times show a similar intestinal organism. The organism seen after feeding on trench fever patients has been called *Rickettsia wolhynica* while that seen in apparently normal lice has been called *R. pediculi*.

There is considerable evidence that *R. wolhynica* and *R. pediculi* are one and the same organism,³⁴ and that this organism is the cause of trench fever. Confirmatory evidence, however, is lacking. Attempts to propagate the organism in experimental animals and in bacteriologic media of many types have failed. It seems best, therefore, to regard *R. wolhynica (pediculi)* as the probable but incompletely established cause of trench fever.

Pathologic Lesions.—Since the disease is not fatal, and has not been transmitted to animals, nothing is known concerning the internal lesions except that the spleen is enlarged to palpation. Biopsy of the cutaneous lesions shows peri-vascular lymphocytic infiltration and hyperplasia of the capillary endothelium, but no specific changes.

Clinically, the disease shows a sudden onset with severe headache, chills, and fever, and anorexia. Pain and tenderness in muscles and bones are particularly characteristic. A macular red rash appears a few hours after the onset of fever. The course of the disease is variable. Irregular recurrent attacks of fever of variable duration occur over a period of weeks, and relapses several months after the initial attacks are not uncommon. The disease is disabling but not fatal.

Laboratory Diagnosis of Rickettsial Diseases

For the definite identification of rickettsial diseases, several procedures may

be utilized.³⁵ The most conclusive evidence is furnished by isolation in animals. Blood from patients should be injected into guinea pigs during the first week of fever.

Typhus produces a febrile but nonfatal illness in the guinea pig. In murine typhus, and also in some epidemic strains, scrotal swelling occurs, and intracellular rickettsiae are present in large numbers in

mushi disease is fatal for mice and guinea pigs, and rickettsiae are readily found in the serous or mucoid peritoneal exudate. In Q fever, guinea pigs may show little evidence of illness, but, when killed after a week or ten days, many rickettsiae may be found in the copious peritoneal exudate. The final identification of all of these rickettsial diseases depends on cross immunity tests with known strains.

Fig. 202.

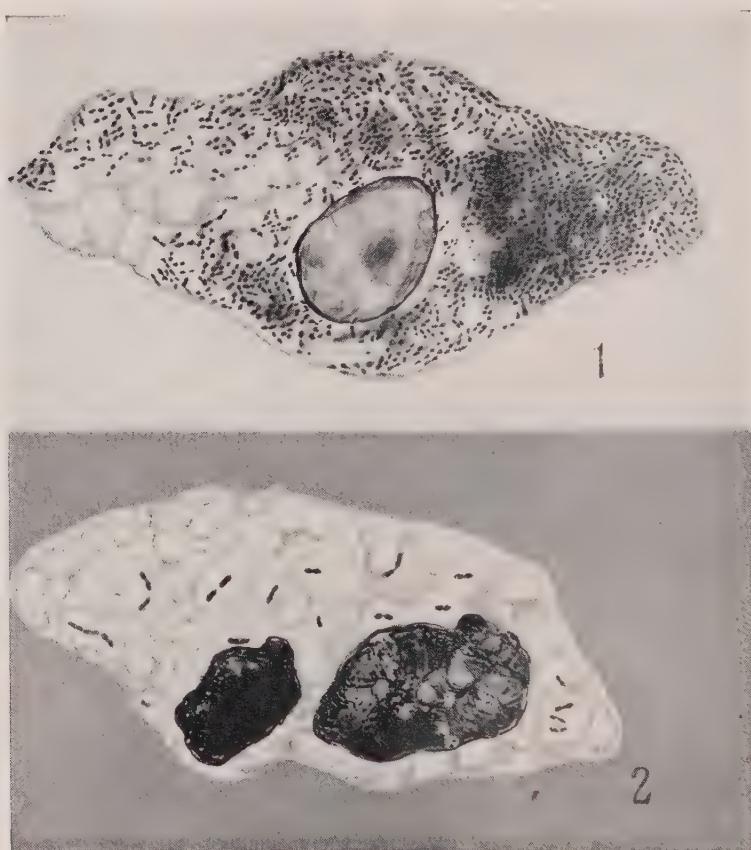


Fig. 203.

Figs. 202 and 203.—The differential diagnosis of typhus and spotted fever in Giemsa-stained smears from the scrotal sacs of infected guinea pigs. The spotted fever rickettsiae are characteristically present in smaller numbers, somewhat larger, and more diffusely distributed. (From Berkovitz, Clinical Tropical Medicine, Paul B. Hoeber, Inc.)

Giemsa-stained smears made from the exudate which forms in the scrotal sac (Fig. 202). In some strains of spotted fever a similar scrotal reaction occurs, but in highly virulent strains, which often are fatal for guinea pigs, the scrotum becomes gangrenous. Spotted fever rickettsiae are found in small numbers in the scrotal sac exudate (Fig. 203). Tsutsuga-

Precautions should be taken against laboratory infection in all cases. The attempted isolation of *R. burneti* is not recommended for routine use because of the danger of spread among laboratory workers.

The complement fixation test also has great diagnostic value.³⁶ Agglutination tests, using concentrated suspensions of

rickettsiae grown in the fertile egg, have also been used successfully. These two tests are of value in differentiating human and murine typhus, and in identifying the various strains of spotted fever.

The Weil-Felix reaction, an agglutination test using as antigens certain strains of *Bacillus proteus* recovered from typhus patients, has long been used as a diagnostic aid. Although *B. proteus* has no etiological relationship to any rickettsial disease, the titer of agglutination is high. In typhus, agglutination in high titer is obtained characteristically with *B. proteus* OX19, while in tsutsugamushi disease the principal agglutinins are against the OXK strain. In spotted fever, agglutination of both strains in relatively low titer is usually found.

Biopsy of the skin has been employed as a method of diagnosis. After fixation in Regaud's fluid and staining by the Giemsa method, rickettsiae may be seen in the vascular endothelium, and in spotted fever also in smooth muscle cells of the arteriolar walls. The recognition of rickettsiae, and particularly their differentiation from mast cell granules, requires experience.

of these organisms. The method which has proved most practical is that first described by Cox.³⁷ Rickettsiae are injected into the yolk sacs of fertile eggs, where they grow massively within the entodermal cells which line the sacs. After several days, the yolk sac membranes are harvested, and the rickettsiae are freed from their host cells and from the surrounding yolk to form the emulsion used for vaccination.

The effectiveness of such vaccines against typhus and spotted fever is definitely established. Cases occur after vaccination, but they are usually mild. Vaccination against Q fever probably is also effective. A satisfactory vaccine for tsutsugamushi disease has not yet been prepared. *E. tsutsugamushi* grows in the yolk sac, but for some reason the organisms are not sufficiently antigenic to build up satisfactory immunity.

BARTONELLOSIS (CARRION'S DISEASE)

Organisms of the genus *Bartonella* are morphologically similar to the rickettsiae and are carried by arthropods, but differ from them in so many other ways that most authorities do not include them in this group. They are discussed here for the sake of convenience. The best-known representatives of the group are *B. bacilliformis*, *B. muris*, *B. canis*, and *B. tyzzeri*, which are found in human beings, rats, dogs, and guinea pigs, respectively.³⁸ Each species of *Bartonella* is specific for the animal in which it occurs. The organisms infect and destroy the red

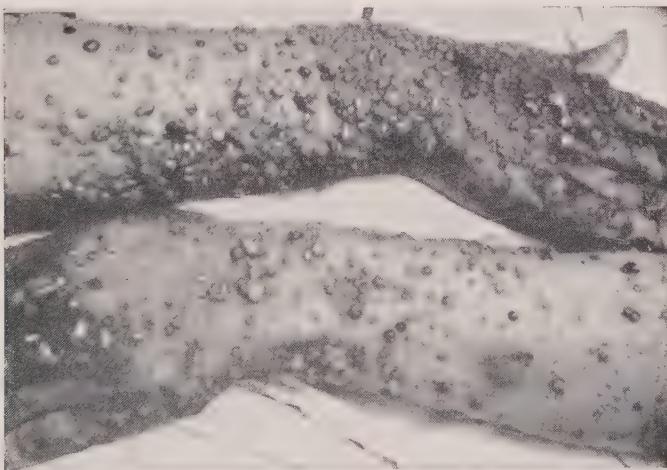


Fig. 204.—The miliary cutaneous eruption of verruga peruana consists of rounded, elevated coalescing nodules of various sizes favoring the extensor surfaces of the extremities. (From Ash and Spitz, Pathology of Tropical Diseases, W. B. Saunders Co.)

Vaccination

Immunity after recovery from rickettsial diseases is usually absolute for the remainder of the individual's life. It is said, however, that second attacks of tsutsugamushi disease may occur.

In spite of our inability to cultivate rickettsiae in cell free media, many ingenious methods have been devised for obtaining large concentrations

blood cells, producing severe and often fatal anemia under certain conditions. Although *B. bacilliformis* appears chiefly as an intracellular parasite in human tissues, it can be freely cultured extracellularly in special types of media.³⁹

Bartonella infection in lower animals is of peculiar interest because of the relationship of the spleen to its development. Ordinary

laboratory strains of the white rat are latently infected, even though they show no anemia or other evidence of illness and no organisms can be seen in the blood. When such rats are splenectomized, severe anemia with organisms in the red blood cells occurs, and results fatally in

more than half of the rats. The mechanism by which the intact spleen inhibits the development of clinical bartonella infection has not been determined.

Carrión's disease in man is found only in Peru, Ecuador, Chili, and Colombia. It is

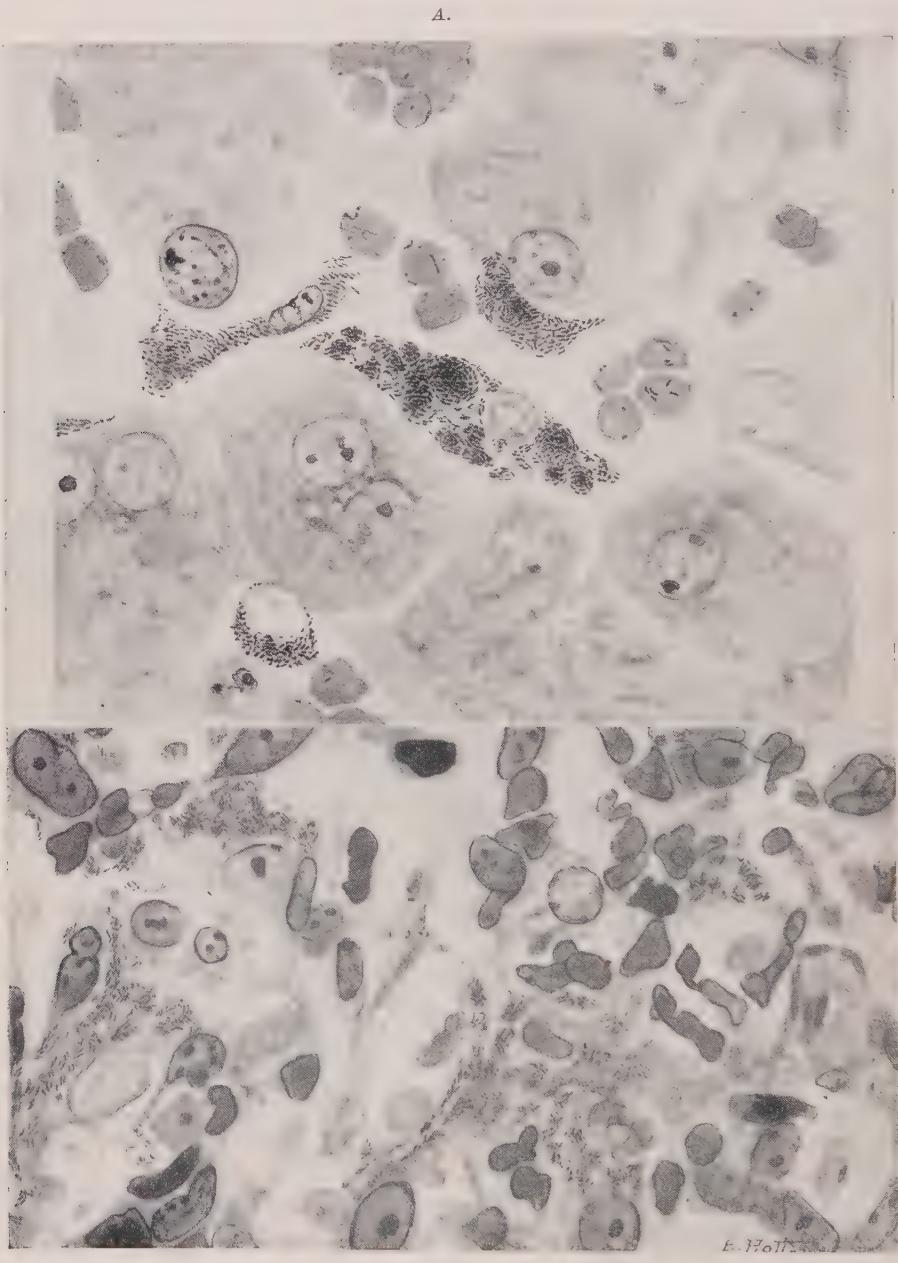


Fig. 205.—A, Liver from a fatal case of Oroya fever (anemic form of Carrión's disease), showing *Bartonella bacilliformis* in Kupffer cells and also in the red blood cells. (Regaud fixation and Giemsa stain.)

B, Cutaneous nodule from a case of verruga peruana (cutaneous form of Carrión's disease), showing *Bartonella bacilliformis* in the proliferating endothelial cells. (Regaud fixation and Giemsa stain.)

(From Berkovitz, Clinical Tropical Medicine, Paul B. Hoeber, Inc.)

carried by at least two species of sandflies of the genus *Phlebotomus*. Intermediate mammalian hosts have not been discovered. It is characterized clinically by two rather divergent types of illness, with intermediate cases which share the features of each type. One type, known as Oroya fever, apparently occurs in individuals with little resistance. It is a rapidly progressing febrile anemia, which often terminates fatally in four to twenty-one days. Nearly every erythrocyte is affected, and the red count is commonly below one million. The anemia is of the macrocytic type, but does not respond to liver extract, and no effective chemotherapeutic agent has been announced, although aureomycin and terramycin are effective in murine bartonellosis.⁴⁰

The second type of the disease (*verruga peruviana*) is characterized by the development of multiple cherry-red cutaneous nodules, 2 to 20 mm. in diameter, which are located chiefly on the extremities and face (Fig. 204). Individuals with this type of the disease may show little or no clinical evidence of illness. Frequently, however, several weeks after recovery from a period of mild or moderately severe febrile anemia, during which bartonellae were seen in the erythrocytes, the nodular cutaneous form of the disease may make its appearance. It is clear that these two lesions, the anemic and the cutaneous, are stages in a single disease, the cutaneous phase probably representing an allergic reaction to the organism.

The pathologic lesions in fatal cases are those of a severe infectious anemia. The skin and conjunctivae may have an icteric tinge. There is generalized red hyperplasia of the bone marrow, fatty infiltration of the liver, and generalized lymph node enlargement. The reticuloendothelial cells throughout the body, notably in spleen, lymph nodes, and bone marrow, including the Kupffer cells of the liver, are crowded with bartonellae, which tend to form spherical clusters in the cytoplasm⁴¹ (Fig. 205.) Degeneration of the kidney tubules, similar to that seen in blackwater fever, may be seen. The cutaneous lesions are soft and deep red on cut section. Microscopically the picture resembles that of a rapidly growing capillary hemangioma, with numerous mitotic figures. *Bartonella bacilliformis* is usually present in large numbers in the endothelial cells of such lesions in Giemsa-stained sections. (Fig. 205.) The production of lesions with such definitely neoplastic features by an intracellular parasite, in relatively immune individuals, is of particular interest.

The laboratory diagnosis of the disease is readily made in the anemic stage by finding the organism in the red cells in Giemsa-stained blood smears. Blood culture, using special media, is positive in all stages of the disease, and for several months or years after recovery.

VIRAL DISEASES

The field of virology has expanded with amazing rapidity in recent years, and virologic research, interdigitating with cytology, biochemistry, and cellular physi-

ology, has been an important factor in the development of new concepts of the basic phenomena of life, growth, and reproduction. In a textbook of pathology, discussions of viral diseases are necessarily abbreviated, and for more detailed information, the student is referred to recent texts such as that edited by Rivers,⁵ and that by van Rooyen and Rhodes.⁶

This section will include most of the diseases of man which are of proved viral etiology, and a few, such as postinfection encephalitis, in which the evidence for causation by a virus is not conclusive. Certain viral diseases will be considered in other chapters.

Evidence that a virus causes a disease is most conclusive when the virus can be transmitted to animals and grown on fertile egg membranes, and when the characteristic lesions of the disease can be produced in animals after passage through several series of eggs. In such cases, the essential features of Koch's postulates have been fulfilled.

The transmission to human volunteers, by material passed through porcelain filters, and the constant occurrence of certain types of specific intracellular inclusions are criteria which may strongly indicate viral etiology. Molluscum contagiosum, for example, is universally accepted as a viral disease, although its agent has not been shown to infect animals or fertile eggs.

The term virus, formerly used in the broad sense to mean any "infective agent," is now restricted to filter-passing agents with certain characteristics which will be discussed presently. It has become synonymous with the older terms "filtrable virus" and "ultramicroscopic virus." Filtrability depends on a number of factors other than the size of the filter pores and the dimensions of the particles. It is, however, generally true that viruses pass through unglazed porcelain filters, while bacteria and rickettsiae (with few exceptions) do not. The term "ultramicroscopic" has become almost meaningless with the advent of the electron microscope. It is obvious that both terms, being only inaccurate methods of denoting size, are unsuitable as criteria for classification.

The Nature of Viruses.—The interrelation of bacteria, rickettsiae, and viruses has already

been considered in the introduction to this chapter, and it has been said that the boundaries of these three groups are not sharply defined. The rickettsiae and some of the larger viruses are barely large enough to be seen with the ordinary microscope (0.3 to 0.25 micron)

limiting cytoplasmic membranes similar to those of bacteria and rickettsiae.¹ Vaccinia virus bodies also resemble bacteria in chemical and antigenic composition.

Within the group of viruses there is great variation in the degree of dependence upon the

COMPARATIVE SIZES OF VIRUSES

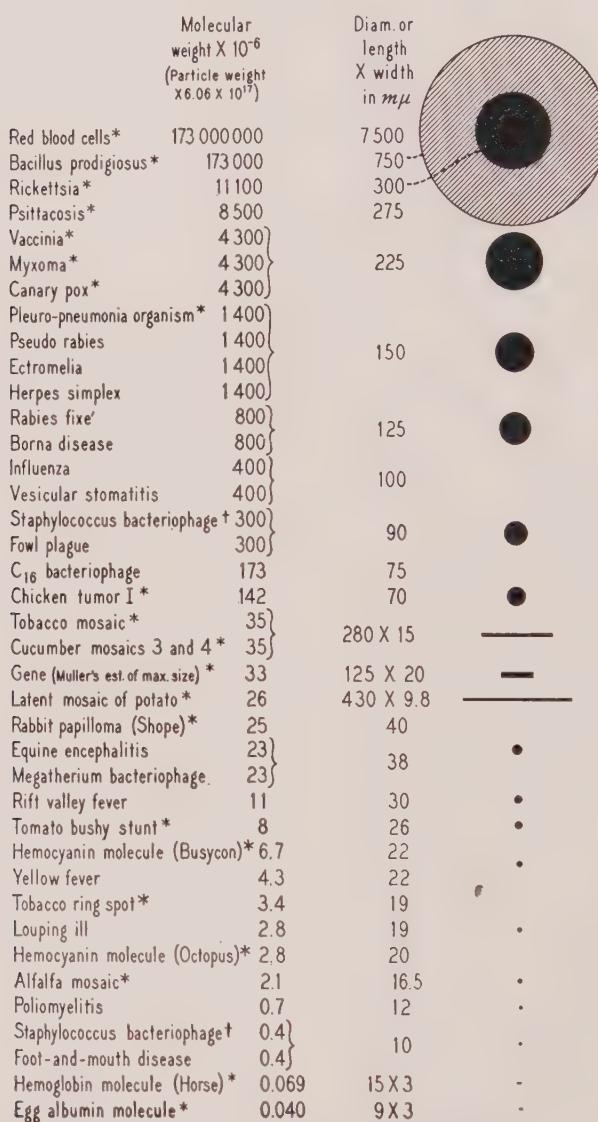


Fig. 206.—Comparative size of bacteria, rickettsiae, and viruses. (Courtesy Dr. W. M. Stanley.)

while the smaller viruses range downward to 0.008 micron in smallest diameter and are for the most part beyond the range of the ordinary microscope (see Fig. 206). Many viruses have been seen clearly with the electron microscope. The elementary bodies of certain larger viruses, such as that of vaccinia, have cell walls and

host cell for metabolic processes. The larger viruses contain enzymes which allow them to carry on some independent metabolic activity. The smallest viruses, which approach molecular size, may be completely dependent on the enzymes of the cells in which they live. Certain plant viruses and perhaps some viruses

which infect animals are "autocatalytic" proteins, which can be purified and crystallized like true chemical compounds.⁴² Although capable of reproduction, in the sense that they increase in amount of living tissues, they lack other attributes of living organisms. Reproduction is by a process quite unlike that of cell division, apparently depending on the ability of these large protein molecules to catalyze enzymatic reactions in their host cells, as a result of which other identical protein molecules are formed. Much of our knowledge of viruses has been acquired by the study of plant viruses and bacteriophages. Morphologically, viruses vary in shape as well as size; some are coccoid, some rod-shaped, and others tadpole-shaped, ovoid, or cube-shaped.

mice. (3) The formation of inclusion bodies (see discussion below). (4) a tendency to lie dormant in tissues (latent or inapparent infection) for long periods of time, without producing symptoms or lesions. Such latent viruses may cause serious illness in a host of a different species or in their original hosts if resistance is lowered by dietary deficiency⁴⁴ or if tissues from one animal are injected into another. An interesting example of a latent virus activated by repeated tissue injection is virus III which Rivers encountered in the testicle of the rabbit. Observations such as this have taught virologists to be very cautious in their interpretation of inclusions seen in the tissues of animals injected with human material. (5) Rapid variation in pathogenic properties, and adaptation to new

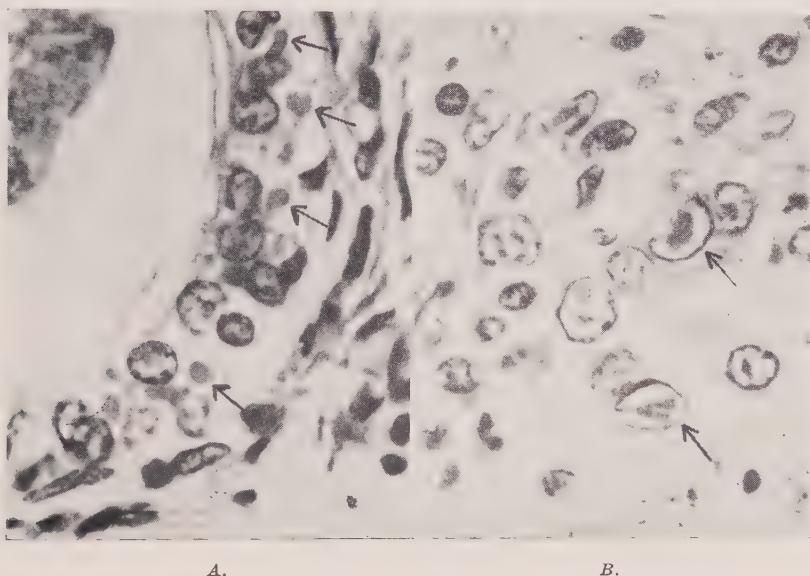


Fig. 207.—A, Cytoplasmic inclusions in bile duct epithelium (canine distemper). B, Nuclear inclusions in intestinal mucosa (feline agranulocytosis).

As a result of intensive recent investigation in the field of viruses, much has been learned concerning the important problems of host-parasite relationships, which may eventually help in understanding the phenomena of neoplastic growth. Some success has been achieved in inhibiting the synthesis of viral proteins by the use of metabolic antagonists (inactive analogues of vitamins and essential amino acids.) The discovery that some neurotropic viruses are oncolytic, localizing in and destroying certain malignant tumors in experimental animals,⁴³ is of particular interest.

Characteristics of Viruses.—The important properties of viruses may be summarized as follows: (1) *Filtrability* (discussed above). (2) *Cytotropism*. Viruses live and multiply only within cells; often only within certain types of cells and in certain species of animals. The virus of poliomyelitis, for example, is specifically adapted to growth in the ganglion cells of the spinal cord, and has been transmitted only to monkeys and, in the case of certain strains, to cotton rats and

conditions. Yellow fever virus, for example, when injected intracerebrally in young mice, produces encephalitis, and loses its ability to cause fatal hepatitis in monkeys. It is said to have become "neurotropic." (6) Viral infections, which in themselves have little or no mortality, may be accompanied or followed by severe and fatal bacterial infections. In such cases, the bacterial infection may be the apparent cause of death, and the underlying and conditioning viral infection may be discovered only by careful study. (7) Viral infections generally do not respond to chemotherapeutic agents such as the sulfonamides and penicillin. Although these agents probably do not penetrate cells, viruses are vulnerable during the brief period when they are passing from one cell to another. The only viruses known to respond to chemotherapeutics (those of lymphopathia venereum, psittacosis, and trachoma) are relatively large and may have some independent metabolic activity which may be blocked by the therapeutic agent.

Viral Inclusion Bodies.—In association with many but by no means all viral infections, visible structures known as "inclusion bodies" are seen in the infected cells.^{45, 46, 47} These bodies occur either in the cytoplasm or in the nucleus, and in some cases in both. They vary considerably in size and shape, but usually are roughly spherical and their average size is about that of the erythrocyte. They tend to be eosinophilic with most staining methods, and to be surrounded by a clear zone in the nucleoplasm or cytoplasm in which they are embedded. Their internal structure ranges from granular to homogeneous.

Starting at the upper end of the scale, there can be little doubt that large viruses such as that of psittacosis are living organisms, which can be seen as individuals. In infected tissues, "elementary bodies" only slightly smaller than rickettsiae are present in large numbers. These bodies tend to be grouped in the cytoplasm in spherical clusters resembling those formed by *Bartonella bacilliformis*, and *Rickettsia burneti*. Since psittacosis is customarily (and somewhat arbitrarily) regarded as a viral disease, these bodies are called "elementary bodies," and their aggregated colonies are called "inclusion bodies." Goodpasture⁴⁸ was sufficiently convinced of the microbial nature of the elementary bodies which compose the inclusion body associated with smallpox to give them a name (*Borrelia variolae hominis*). Similarly, the elementary bodies of the psittacosis virus have been called *Microbacterium multiforme psittaci*.⁴⁹ Rivers has characterized such bodies as "the midgets of the microbial world."

In the case of small viruses, the inclusion bodies are homogeneous. There is difference of opinion regarding the nature of these uniformly staining structures. Some believe that they are composed of elements like the elementary bodies of psittacosis or the intracellular colonies of rickettsiae described above. In this case, their lack of apparent internal structure is explained by the assumption that the elementary bodies are too small or too closely packed to be seen as individuals. (Colonies of streptococci in agar appear homogeneous at low powers of magnification.) Others believe that they are products of degenerated cytoplasm or nucleoplasm, while another view is that they are composed of both elementary bodies and cytological constituents. Probably all three views are correct in individual instances.

The formation of those inclusion bodies which are aggregates of small elementary bodies may depend to some extent on the development of cellular immunity. Inclusions are absent in many viral diseases. Elementary bodies of small size uniformly distributed in a cell would escape detection, but the clumping of such bodies (analogous to the agglutination of bacteria) results in large masses which are readily seen.

Structures greatly resembling viral inclusion bodies are occasionally seen in tissues damaged by chemical poisons of various types. We can only say, therefore, that some of the viral inclusions are colonies of minute biologically simplified microorganisms, while the nature of the homogeneous inclusions associated with small viruses has not yet been determined.

Epidemiology of Viral Infections.—Many viral diseases, like bacterial infections, are transmitted by contact, by droplet infection, or by ingestion. Insect transmission is more common in viral than in bacterial infections. Intermediate hosts among lower animals are also rather more common in viral than in bacterial infections, and it has been found that diseases of man may be contracted from birds as well as from mammals. Host relationships often are complex. Equine encephalitis, for example, though probably carried from the horse to man by mosquitoes, is also found in birds⁵⁰ and its original or natural habitat is difficult to determine. Lymphopathia venerum is the only important viral infection of man which is transmitted by coitus. Insect-borne viral diseases are transmitted to man "biologically," that is, by living and multiplying in insect tissues, in contrast to the purely mechanical transmission of typhoid bacilli, for example, by flies.

Immunity in viral diseases is both humoral and cellular. Recovery from most viral diseases of man and animals confers solid and lasting immunity. Exceptions are to be noted however, notably the common cold, herpes simplex infection, and influenza. There is some evidence that viruses persist in the body after recovery, so that immunity may be the "immunity of tolerance." Neutralizing antibodies appear in the blood after recovery, and in some instances, also, complement fixing, precipitating, and agglutinating antibodies. The ability of viruses to persist in the body after recovery from acute infection perhaps depends on their intracellular location, which protects them from the destructive effect of humoral antibodies. Immune serum can only act on a virus which is in the process of passing from one cell to another.

Because of the intimate relationship of viruses to the metabolism of their host cells, immunity may be raised or lowered by nutritional changes, endocrine disturbances, and other factors which stimulate or inhibit the activity of intracellular enzymes.

Successful vaccination is possible against a number of viral infections. Killed virus is usually ineffective. Results are obtained in most viral diseases only by the use of living but attenuated strains of virus, which produce mild infection. Attenuation may be achieved by passage through animals or by cultivation in tissue cultures or in fertile eggs. The principle involved is identical with that discovered by Jenner following his classical observation that milkmaids who became infected with cowpox (attenuated smallpox) were immune to virulent smallpox.

Methods for the Study of Viruses.—All methods available for the propagation and study of viruses require the presence of living or at least surviving cells.^{51, 52} The simplest method is the inoculation of laboratory animals. Rabbits, guinea pigs, mice, rats, and ferrets are most often used. Monkeys are indispensable for certain viruses. Intracerebral and intranasal injection are often used, but intratesticular injection and injection into the cornea

and anterior chamber of the eye have also proved useful, as well as injection by the common intraperitoneal and subcutaneous routes. After isolating a virus by animal inoculation, it may be transmitted serially and identified by crossed immunity tests with known strains of viral disease and by other immunologic tests. The blood serum of patients may also be tested for the presence of antibodies which neutralize known viruses. Viruses may be studied in tissue cultures of susceptible cells, and in recent years the chorioallantoic and yolk sac membranes of fertile hen eggs, as well as the embryo itself, have been used extensively for both the isolation and the propagation of certain viruses.^{6, 53} Media of the Maitland type, consisting of minced tissue suspended in a mixture of serum and Tyrode's solution, have also proved useful. In the latter types of media the tissue cells do not multiply, but continue to metabolize for about two weeks.

Most viruses remain viable for weeks or months in tissues which are frozen rapidly and maintained at minus 20° C., or at lower temperatures. Long survival is often possible also if tissues are placed in neutralized glycerin and kept at ordinary refrigerator temperatures. Whenever tissues are suspected of harboring a virus, they should be preserved by one of these methods, and if histologic examination indicates later that a virus may be present, attempts to isolate the virus may then be made.

Pathologic Lesions Caused by Viruses.—The range of lesions caused by viruses is at least as great as that caused by bacteria.⁵⁴ Acute necrosis, chronic proliferative granulomatous lesions, and various intermediate types of reaction are seen. The proliferative type of reaction in its most striking form is represented by certain viruses which are the apparent causes of benign and malignant tumors in lower animals.⁵⁵ The most characteristic lesions, when present, are the inclusion bodies, and the pathologist should have some experience in recognizing these structures, since they often furnish the only clue to the correct diagnosis, and are commonly overlooked unless specifically searched for.⁴⁷

Classification of Viruses.—No adequate criteria are available for the accurate classifica-

tion of viruses. They have been classified on the basis of the reactions which they evoke (necrotizing, lytic, granulomatous, and neoplastic), and on the nature of the inclusions (if any) which are associated with them. Another general classification is based on their affinities for certain types of tissues (epitheliotropic, neurotropic, mesodermotropic, and pantropic). Eventually, a classification based on their metabolic activities will probably be worked out.

In this discussion viruses are grouped on the basis of the organs or tissues in which the most conspicuous lesions are seen. This is done for the sake of convenience and with the realization that generalized invasion of the body is probably more common than has been believed in the past.

Viral Diseases of the Central Nervous System

The group of viral infections involving primarily the central nervous system includes several diseases of considerable clinical importance. They are often called the "viral encephalitides." Encephalitis is the term applied to inflammation of the brain, regardless of its etiology, while myelitis means inflammation of the cord. Many viruses cause lesions in both the brain and the spinal cord (encephalo-myelitis). See also discussion in Chapter 44, page 1324.

In several types of encephalitis and encephalomyelitis a viral etiology has been established by transmission to animals, while other types are of suspected but unproved viral etiology. Some of the latter types will be discussed here because of their pathologic similarity to proved viral diseases.

From the standpoint of histopathology, viral diseases of the nervous system fall into four main groups. In group I, the primary lesion is invasion and destruction of the neurons of the gray matter. Group II is characterized by a primarily meningeal (mesodermal) reaction, and in man is represented by lymphocytic choriomeningitis and possibly also by mumps. The viruses of lymphopathia venereum, vaccinia, and salivary gland disease of guinea pigs, when injected intracerebrally in animals, also cause a reaction which is mainly meningeal. Group III includes a number of types of encephalitis of disputed etiology which follow various infections, and in which the chief lesion is perivascular demyelination. Group IV is exemplified by fox encephalitis, in which

vascular endothelium in the brain is primarily invaded, and inclusion bodies are seen exclusively in these cells. No example of the group IV type of reaction to a virus has been described in man, but it will be recalled that rickettsiae cause encephalitis by involving vascular endothelium.

Most viral infections of the nervous system are characterized by primary damage to neurons (group I reaction above). Histologic reactions are inflammatory in nature, and although there are minor variations in the nature of the reaction, pathologic lesions are unsatisfactory criteria for diagnosis and classification.

Grossly, one often sees petechial hemorrhages into the brain and cord tissue, congestion of the meningeal vessels, and flattening of the cerebral convolutions as a result of edema. Microscopically, the earliest degenerative changes in the ganglion cells are difficult to recognize. The Nissl bodies often disappear as a result of relatively mild injury. Hyperchromatism, fragmentation and lysis of nuclei, especially when accompanied by the accumulation of phagocytic cells around injured cells (neuronophagia), are indicative of cell degeneration. The macrophages of the central nervous system are derived from microglia cells, which are of mesenchymal origin. Ganglion cells showing chromatolysis, loss of nuclei, and other degenerative changes may eventually disappear entirely.

The perivascular spaces take the place of lymphatics, which are not present in the brain or cord. In these perivascular spaces edema fluid is seen, and lymphocytes, plasma cells, macrophages, and occasional neutrophiles accumulate in such a way as to form wide bands (perivascular cuffing). The capillary endothelium is often swollen and may proliferate, but rarely leads to the formation of occluding thrombi as it does in the rickettsial diseases.

Most viral diseases of the nervous system are acute in nature. After sudden necrosis, repair by neuroglial proliferation takes place. A type of chronic encephalitis, lasting a year or more, with herpeslike nuclear inclusions has, however, been described (see page 331). In the process of repair, focal collections of

neuroglial cells (glial nodes) become prominent, and a diffuse increase in neuroglial cells may also be noted. Focal areas of demyelination are seen as a result of vascular occlusion, but extensive demyelination is seen only in group III reactions.

RABIES (HYDROPHOBIA)

The virus of rabies is strongly neurotropic. The disease is acquired usually by the bite of a rabid dog, but cats, wolves, skunks, and vampire bats are also capable of transmitting it. Nearly all mammals are susceptible to infection. The virus is introduced into the wound with the saliva and travels slowly along nerves to reach the central nervous system where it causes acute encephalomyelitis. The incubation period varies from ten days to a year or more, depending largely on the distance between the bite wound and the brain, or cord.

Pathologic Lesions.—Grossly the brain, spinal cord, and viscera show congestion, and petechial hemorrhages may be seen. Rarely the presence of the characteristic inclusions (Negri bodies) may be the only evidence of the disease. Most frequently one finds foci of ganglion cell degeneration, with the consequent accumulation of large phagocytic cells, lymphocytes, and neuroglial cells. Perivascular cuffing, perivascular hemorrhage, and glial nodes are seen in varying degrees in individual cases.^{56, 57}

Cord involvement is most conspicuous when the portal of entry is on the lower part of the body, so that the virus reaches the cord before it has involved the brain. The cranial, spinal, and sympathetic ganglia may be involved.

The inclusions associated with rabies are known as *Negri bodies*. They are most numerous in the hippocampal gyrus, medulla, and cerebellum (Purkinje cells). They are seen best in neurons which have not become necrotic, and probably represent an early stage in the reaction of the cells to the virus. They are said to be absent occasionally in brains from which the virus may be recovered. These inclusions are found only in neurons and are always cytoplasmic. (Plate III.) Several inclusions may be found in the same cell. Their average size is slightly larger than that of the erythrocyte. They are homogeneous except for the presence of a few vacuoles, and eosinophilic by most staining methods. There is no conclusive evidence concerning their precise

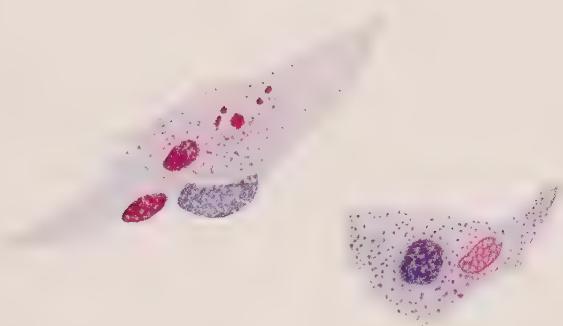


PLATE III.—Negri bodies of rabies. Van Gieson stain. (From Gradwohl, R. B. H., Clinical Laboratory Methods and Diagnosis, The C. V. Mosby Co.)

nature. Goodpasture⁵⁸ believes that they are formed by the fusion of neurofibrillae, but the participation of elementary bodies or virus protein in their formation has not been disproved. The virus of rabies is relatively large (0.125 micron in least diameter).

Rabies in the Dog.—Diagnosis of rabies in the dog is of great importance because of the almost universal practice of giving the Pasteur treatment, if a positive diagnosis is made, to all individuals who have been bitten. The dog should be captured alive and kept under observation. If it has rabies, death will occur within ten days. The diagnosis, which is based on the presence of Negri bodies in the brain, should be made by one experienced in their recognition. Intracranial injection of emulsified dog brain into mice may give a positive diagnosis in some cases in which direct examination of the brain gives negative results.⁵⁹

The Pasteur treatment is based on vaccination with living virus, attenuated by passage through the rabbit and by drying. The long incubation period (in most cases) allows time for immunity to develop before symptoms of the disease appear. With the onset of symptoms, no treatment is of value, and the disease is always fatal. The value of the Pasteur treatment has been challenged,⁵⁶ but on the whole the evidence that it is effective is excellent. Death from treatment is extremely rare, and about 16 per cent of those bitten by animals proved to have rabies develop the disease if treatment is not given.

POLIOMYELITIS

Poliomyelitis, or infantile paralysis, is an acute viral infection occurring chiefly but not exclusively in young children. It rarely occurs in infants under 1 year of age. The relative immunity of adults is largely the result of mild, or atypical and unrecognized infection in earlier life.⁶⁰ Although there is evidence that the virus is not strictly neurotropic, the most important lesions are located in the central nervous system.

Clinically the disease is variable in its manifestations. In its most characteristic form there is an initial period of one to three days during which fever, headache, throat soreness, drowsiness, irritability, gastrointestinal symptoms, and stiffness of the neck are prominent. This is followed by the paralytic stage, as a result of damage to the anterior horn cells.

Bulbar involvement may occur, with involvement of the cranial nerves, and respiratory paralysis is the commonest cause of death. Cerebral and cerebellar involvement is also occasionally seen.

Abortive cases, without paralysis, are believed to be about six times as common as the cases in which paralysis occurs. Such cases are difficult or impossible to recognize on clinical grounds alone, since they simulate minor gastro-

intestinal or respiratory infections from other causes. The presence of poliomyelitis virus in throat washings from children with such mild and atypical cases has been demonstrated by injection into monkeys.⁶¹

Etiological Agent.—The virus of poliomyelitis has been recovered from the brain and cord in fatal human cases, but not from the spinal fluid or blood. The disease is transmissible to monkey,⁶² and in the case of certain strains to cotton rats⁶³ and from these animals to mice.⁶⁴ In these experimental animals, localization occurs in the central nervous system, with the production of clinical and pathologic pictures like those found in man.^{65, 66} Several antigenically different strains of the virus have been described, and certain strains have been propagated in tissue cultures of human embryonic muscle.⁶⁷ Embryonated eggs have not been infected.

Epidemiology.—Poliomyelitis occurs in endemic or epidemic form in the late summer and autumn, but sporadic cases are seen throughout the year. It has been shown that convalescents and even individuals who have shown no signs of illness may be carriers of the virus. Neutralizing antibodies are present in the blood of most adults, whether or not they have had any illness suggestive of active infection.⁶⁸ Thus, epidemics may be initiated from time to time from live virus constantly present in certain carriers, but outbreaks are usually limited in severity because of the fact that most individuals in a community are immune. The possibility of a virus reservoir in mice has been suggested.⁶⁹

The mode of transmission has been intensively studied in recent years, but complete unanimity of opinion has not been attained. In monkeys injected intranasally, there is evidence that the virus reaches the brain by the olfactory nerves. In man, this route of infection apparently is rarely if ever followed, and the high concentration of the virus in the intestinal contents suggests that infection may take place by the gastrointestinal route, as in typhoid fever. The virus has been isolated from sewage,⁷⁰ and also from flies.⁷¹ Transmission by biting insects has long been regarded as a possibility but has not been established definitely in spite of many studies of this problem. Droplet infection is still considered by some workers to be the most important means of transmission.

Tonsillectomy, carried out within three months, is considered to be an important predisposing factor,⁷² apparently resulting in the bulbar form of the disease, and operations on the nose and throat, as well as tooth extractions, are best performed during interepidemic periods. It is also believed that violent exercise tends to precipitate the disease.⁷³

Pathologic Lesions.—Lesions are most conspicuous in the spinal cord and brain. Grossly the brain and cord are swollen and there is congestion of the meningeal vessels. Small petechial hemorrhages are seen on cut section. Minute necrotic lesions may be seen with difficulty by

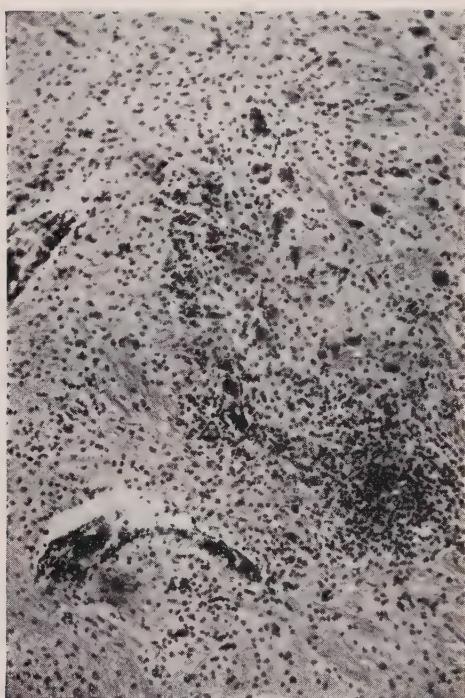


Fig. 208.—Poliomyelitis. Focal and diffuse inflammatory cell infiltration in the anterior horn of the spinal cord. (From Anderson, Synopsis of Pathology.)

using a hand lens. Even when the symptoms have suggested localized involvement of the nervous system, histologic lesions of variable severity are usually found to be widespread, and a completely descriptive term for the average fatal case would be polio-myelo-meningo-encephalitis.

Microscopically, the ganglion cells in the involved areas, most characteristically the anterior horns of the spinal cord, show chromatolysis and other degenerative changes. In the early stages of infection, inclusion bodies have been described in the affected ganglion cells,⁷⁴ but these are rarely present in routine human post-mortem material. The necrotic ganglion cells often are surrounded and partially dissolved by macrophages and neutrophiles. Frequently ganglion cells disappear entirely, and sections of the cord at certain levels may show complete absence of ganglion cells from the anterior horns. Perivascular cuffing with mononuclear cells and occasional neutrophiles and microscopic hemorrhages into the perivascular spaces are seen. Focal and diffuse pro-

liferation of neuroglial cells is seen in the process of repair. Scattered neutrophiles are almost always present, either around degenerating ganglion cells or in the diffuse or focal collections of inflammatory cells.

Certain segments in the cord are involved more severely than others, and lesions may be present in the medulla, cerebrum, and cerebellum. In the so-called "superior" type of the disease, the brain may be more extensively involved than the cord, and the differential diagnosis of these cases from other types of encephalitis may be impossible without virus isolation or immunologic evidence. The presence of neutrophiles in significant numbers is strong evidence against the diagnosis of lethargic encephalitis, but does not exclude equine encephalomyelitis. A few lymphocytes are usually found in the meninges. Peripheral nerves corresponding to degenerated ganglion cells show swelling and fragmentation of the axis cylinders and myelin sheath degeneration. The paralyzed muscles in recovered cases show atrophy and replacement by fat and connective tissue.

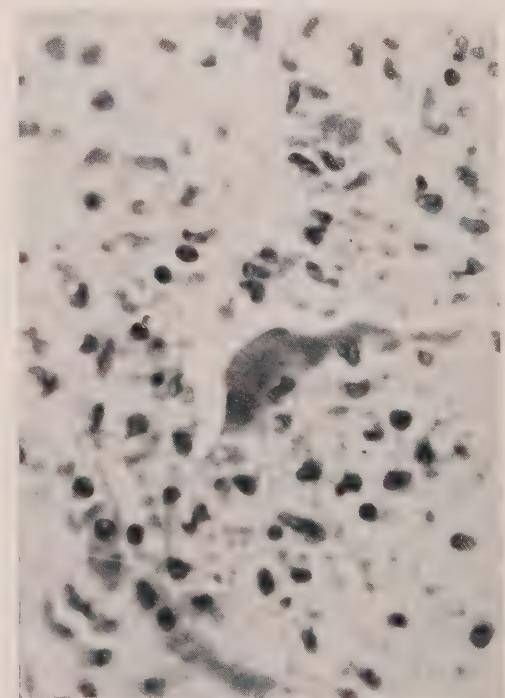


Fig. 209.—Poliomyelitis. A degenerating neuron in the anterior horn, surrounded by inflammatory cells, some of which are neutrophiles.

Lesions outside of the nervous system are less striking. There is generalized lymph node enlargement, and on section one finds petechial or diffuse hemorrhage. Microscopically, there is lymphoid hyperplasia. The spleen is often slightly enlarged, and there is cloudy swelling of the liver and kidneys.

Clinical Pathologic Correlation.—In typical cases with principal involvement of the anterior horns of the cord, one finds the "lower motor neuron lesion," flaccid paralysis of scattered groups of muscles. The affected muscles are tender and painful on passive motion. Involvement of the upper cervical cord and medulla, with consequent paralysis of the muscles of respiration and injury to the respiratory center, accounts for most fatalities. In the less common superior type with cerebral involvement, lethargy, stupor, and cranial nerve paralysis are seen, with spastic paralysis of the extremities. Cerebellar involvement, which is rare, causes ataxia and dizziness.

Rigidity of the neck is the result of meningeal irritation. Spinal fluid examination, which is often employed as a diagnostic procedure, shows 10 to 1,200 cells per cubic millimeter; neutrophiles often predominating in the early stages and lymphocytes in the later stages.

Recovery of muscle function during convalescence and thereafter, which often occurs to a surprising degree, is the result of the disappearance of edema in the spinal cord and the hyperplasia of those muscle fibers with innervation still intact. Ganglion cells which are completely destroyed are not replaced.

ENCEPHALITIS LETHARGICA

Encephalitis lethargica (epidemic encephalitis) (Type A encephalitis) (Eckendorf's disease⁷⁸) made its appearance during World War I. Following an extensive epidemic of wide geographic distribution which reached its height in 1919 and 1920, it became endemic in nearly all countries. It was most prevalent in the winter and spring, and affected chiefly adults. Since 1925 it has occurred only sporadically, if at all. Diagnosis is at best doubtful at present, since there are no specific immunologic tests. It should be remembered that the epidemic of lethargic encephalitis occurred before the advent of modern virologic methods.

Etiology.—This type of encephalitis has not been transmitted to animals or grown in fertile eggs. Its viral causation is regarded as highly probable, however, in view of its apparently infectious nature, and its clinical and pathologic similarity to other types of encephalitis of established viral etiology.

Clinical Picture.—The clinical picture is variable.⁸⁰ Excitement or delirium in the early

stages is followed by lethargy and somnolence, with moderate fever, diplopia, and other evidences of cranial nerve paralysis. The mortality during the acute stage is 20 to 40 per cent. The lethargy may clear up, but often persists for months or years. Dementia, paralysis of cranial nerves, sensory disturbances, and other neurologic signs and symptoms may also persist. A common sequela is paralysis agitans or Parkinsonism, characterized by rigid posture, lack of facial expression, and a coarse "pill-rolling" tremor. This clinical picture, which in this case is caused by ganglion cell degeneration in the substantia nigra, occurs also from other causes (see page 1316). Atypical and abortive forms of the disease are believed to occur, but are difficult to diagnose, and the frequency of such cases is not known.⁸⁰

Pathologic Lesions.—Grossly, as in other types of encephalitis, the only changes seen are petechial hemorrhages and small areas of softening, particularly in the basal ganglia, midbrain, and pons. Microscopically, perivascular cuffing with lymphocytes and macrophages dominates the picture⁸¹ (see Fig. 210). This lesion is present in the perivascular spaces of the large as well as the small vessels, and is most prominent in the areas mentioned above, although changes may be found in other locations. Perivascular hemorrhages and a mild lymphocytic infiltration of the meninges may be seen. Degenerative changes in ganglion cells are present, but are less acute and severe than in poliomyelitis, and neutrophiles are rarely seen. Inclusion bodies are generally absent.

ST. LOUIS ENCEPHALITIS

St. Louis encephalitis emerged as a viral entity in 1933, as a result of the study by modern methods of an epidemic which occurred in St. Louis and in neighboring districts.⁸² Several thousand cases were reported in this epidemic, and the mortality was about 20 per cent. This disease differed from Economo's lethargic encephalitis in several respects: its occurrence in the summer months, the infrequency of serious sequelae, and, most important of all, the fact that it was readily transmitted to mice and to monkeys. Individual cases were indistinguishable clinically from lethargic encephalitis, but the composite picture of the epidemic was appreciably different.⁸³ Minor epidemics have occurred since 1933, and sporadic cases have been reported in various parts of the United States.

The virus, which may be transmitted serially in mice by intracerebral injection, is of relatively small size, having a diameter of 0.030 micron. It is immunologically distinct from all other known neurotropic viruses, but is related to Japanese B encephalitis.

Epidemiologic studies have shown that the virus may be recovered from trapped mosquitoes.

In the suburbs of St. Louis, during nonepidemic periods, chicken mites also have been shown to harbor the virus.⁸⁴ Experimentally, the infection can be transmitted by both of these arthropods and also by ticks. The mode of transmission of the disease in epidemics is not yet definitely known, but it is probably carried by mosquitoes.⁸⁵

Pathologic Lesions.—Grossly the brain shows congestion and edema, with petechial hemorrhages. Lesions are found particularly in the brain stem and basal ganglia, but occur to some extent in all parts of the central nervous system. The microscopic picture is essentially like that of other viral encephalitides.⁸⁶ Degenerative changes in neurons are less striking than in poliomyelitis and about as conspicuous as in lethargic encephalitis.

Japanese B Encephalitis.—Japanese B encephalitis is closely related clinically and pathologically to St. Louis encephalitis, but the two viruses are not completely identical immunologically.⁸⁷ An epidemic of this disease occurred in Japan in 1924 and since then it has become endemic in Japan and China. Japanese B encephalitis, like St. Louis encephalitis, occurs in the spring and summer (in contrast to lethargic encephalitis) and is probably mosquito-borne.⁸⁸

EQUINE ENCEPHALOMYELITIS

Equine encephalomyelitis was carefully studied in lower animals for several years before it was established as a cause of disease in man. It occurs in endemic and epidemic form in horses and in two immunologically distinct types—eastern and the western. The epidemiological complexity of viral diseases in general is well illustrated by this disease. The virus has been isolated from naturally sick pheasants;⁸⁹ ex-

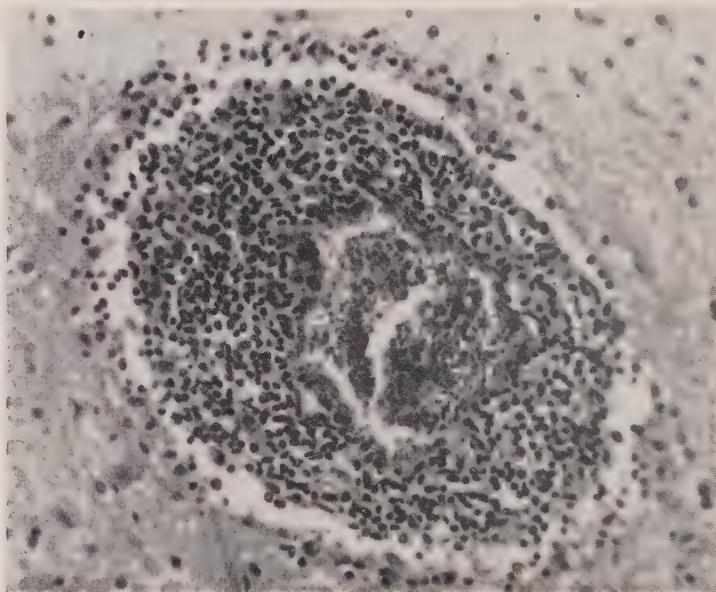


Fig. 210.—Lethargic encephalitis (von Economo type). Perivascular cuffing with lymphocytes.

The other changes include neuronophagia, perivascular hemorrhage, perivascular cuffing with mononuclears, mild meningitis, and focal glial proliferation. It would usually be impossible to distinguish between St. Louis encephalitis and encephalitis lethargica on purely histologic grounds. Inclusion bodies have not been found in the nervous system in St. Louis encephalitis. The significance of occasional inclusions in the kidneys is not clear.

perimentally, it may be transmitted to pigeons, guinea pigs, and mice; its experimental transmission by several species of mosquitoes has been reported; in ticks it not only survives but is passed on to the offspring by infection of the ova. Present evidence suggests that birds are the important reservoir of the disease, and that human beings are infected by mosquito transmission from the horse, while ticks may serve to maintain the infection during the winter months.

The first definite proof of the occurrence of equine encephalomyelitis in man was furnished by the study of an epidemic in eastern Massachusetts in the summer of 1938. Most of the

cases in this epidemic occurred within flying range of mosquitoes from stables where infected horses were kept. Brain tissues, obtained post mortem, were injected into guinea pigs and caused a fatal transmissible disease which was quickly identified by crossed immunity tests as the eastern strain of equine encephalomyelitis.⁹⁰

Clinically the disease affects children primarily, and is characterized by convulsions, fever, neck rigidity, and, in severe fatal cases, by coma. Spinal fluid examination shows 200 to 3,000 cells per cubic millimeter, neutrophiles predominating. Isolated cases may be indistinguishable clinically from St. Louis encephalitis or from the encephalitic form of poliomyelitis, so that virus isolation or a protection test is often necessary for accurate diagnosis. Most children recovering from severe infection with the virus have been left with distressing neurological symptoms, as a result of permanent damage to the brain. In some cases obstructive hydrocephalus develops.

Pathologic Lesions.—Grossly, there are no visible changes other than intense congestion of the meninges, flattening of the convolutions, and minute petechial hemorrhages. Microscopically, inflammatory lesions are seen in all parts of the brain and cord, but are most conspicuous in the basal ganglia, pons, and medulla. The inflammatory reaction usually is more intense and more diffuse than in other types of viral encephalitis.⁹¹ Small foci of actual necrosis of the brain substance are common and such areas are infiltrated with neutrophiles. Perivascular cuffing and definite meningitis are also conspicuous, and neutrophiles predominate in these lesions. Hyaline thrombi may be found in the arterioles. Nuclear inclusions have been described in experimental animals, but not in human brains. No important changes are found outside of the nervous system.

Vaccination.—An effective vaccine has been prepared by cultivating the virus in fertile eggs. The chick embryo itself, as well as the chorio-allantoic and yolk sac membranes, contains virus in high concentration. This vaccine has found its greatest usefulness in protecting horses and mules. It also protects laboratory workers who encounter unusual hazard in handling infective material. The virus is killed by treatment with formalin before being used, so that in this disease we find an exception to the general rule that immunity in viral diseases is possible only by the injection of living virus.

Venezuelan equine encephalitis is an immunologically distinct variety which occurs in horses in South America, and in a few instances has been reported in human beings. It differs from

the other varieties in that the virus is readily recovered from throat washings and from the blood stream.

LYMPHOCYTIC CHORIOMENINGITIS

Lymphocytic choriomeningitis has been established recently as a definite disease of man. Although the number of cases in which the diagnosis of active infection has been made is small, the presence of neutralizing antibodies for the virus in about 10 per cent of a series of 2,000 human sera studied suggests that the virus may often cause subclinical or extra neural infection. The virus is of medium size, and readily transmissible to guinea pigs (in which it causes fatal infection) by the injection of spinal fluid from acutely infected humans. The infection occurs spontaneously in mice⁹² and in monkeys. The method of transmission to man is not known.

The clinical picture in man is that of an acute febrile illness of a few days' duration, with headache, stiffness of the neck, nausea, and vomiting. The mortality is extremely low. The spinal fluid shows a few hundred cells, chiefly lymphocytes, per cubic millimeter. Cases have been reported in which the clinical picture was that of severe generalized infection without striking neurological symptoms.⁹³

Pathologic Lesions.—Pathologic studies in experimental animals have shown that the virus of lymphocytic choriomeningitis invades and causes lesions in many organs other than the brain.⁹⁴ Interstitial pneumonitis similar to that caused by other viral infections is found, and there are small foci of necrosis, probably caused by the presence of the virus, in the liver, kidney, and adrenal. In the brain, there is little evidence of diffuse encephalitis, and the inflammatory cells, which are chiefly lymphocytes, are concentrated in the meninges and in the choroid plexus. The fact that these structures are usually regarded as of mesodermal origin supports the view that the virus is primarily mesodermotropic rather than neurotropic.

The pathologic lesions in man have not been extensively studied because of the low mortality from the disease. From the evidence available, however, it would appear that the human lesions parallel those observed in experimental animals. In neither human beings nor animals has evidence been presented that inclusion bodies directly related to the virus are present. The nuclear inclusions occasionally found in the choroid plexus in mice by Findlay and Stern were believed by these workers to be caused by a concomitant infection with the mouse salivary gland virus.⁹⁵

LYMPHOGRANULOMA VENEREUM ENCEPHALITIS

The virus of lymphogranuloma venereum has been isolated from the spinal fluid of patients with a clinical picture of encephalitis.⁹⁶ In such patients, genital lesions were so inconspicuous that they might easily have been overlooked. The lesions of the condition are not known.

MUMPS ENCEPHALITIS

Encephalitis caused by the virus of mumps is of frequent occurrence. It may occur during or after the salivary gland involvement, or may occur without the usual symptoms of mumps. Some authorities believe that it occurs to some degree in the majority of cases of mumps. It is characterized, like lymphocytic choriomeningitis, by a very high lymphocyte count in the spinal fluid, and the pathologic change is probably chiefly in the meninges. The disease is rarely fatal. It is not to be confused with postinfection encephalitis, to be described later, which also may follow mumps.

RUSSIAN SPRING-SUMMER ENCEPHALITIS

This is a tick-borne disease, which is caused by a virus immunologically distinct from that of St. Louis encephalitis and Japanese B encephalitis. There is some evidence that the virus of this type of encephalitis in Russia may be closely related to that of louping ill,⁹⁷ a fatal tick-borne encephalomyelitis occurring in sheep.

HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis is regarded by most authorities as a distinct entity. Cases have been reported in which the characteristic large nuclear inclusions are found in the brain, and from which the virus has been isolated.⁹⁸ Confirmatory evidence is furnished by an increasing antibody titer, during the course of the disease, against the herpes simplex virus.

Inclusion encephalitis is a term originally applied by Dawson to an unusually chronic form of encephalitis, with progressive mental deterioration over a period of several years. At autopsy, herpeslike inclusions are found in the brain, with extensive diffuse neuroglial proliferation. The relation of this disease to herpes simplex encephalitis is not yet clear.⁹⁹ In the most chronic case, the histopathology resembles that of subacute sclerosing leuko-encephalitis as described by Van Bogaert.

POSTINFECTION (ACUTE DISSEMINATED)

ENCEPHALOMYELITIS

Under this heading must be considered a group of diseases of obscure etiology, characterized by a pathologic picture quite different from that caused by known viruses.¹⁰⁰ This type of encephalitis usually follows some viral infection, but occasionally is a sequel to bacterial infection, or rarely may occur without recognizable antecedent infection. The majority of cases follow smallpox, chicken pox, measles, influenza, and mumps, or occur after vaccination for smallpox¹⁰¹ or rabies.¹⁰²

Etiologically, it has been suggested that the virus of the antecedent disease (or the toxin, in case of a bacterial infection) may be involved.¹⁰³ All attempts to isolate such a virus or toxin have failed. It has also been suggested that some latent virus may be stirred to activity by the antecedent infection, but this theory likewise has received no experimental support. A

lesion comparable to postinfection encephalomyelitis may be produced in monkeys by the repeated subcutaneous injection of brain tissue.¹⁰³ A rather attractive theory is that the reaction in the central nervous system is an allergic one to the antecedent virus or toxin. This is suggested by the latent period between the onset of the original disease and the encephalomyelitis, and to some extent by the nature of the lesions. Again, this theory lacks proof, and the cause of this peculiar type of encephalitis remains a mystery.

Clinically there is evidence of extensive cerebral damage, and the picture may simulate that of the viral encephalitides previously discussed. Fever, headache, vomiting, drowsiness, and convulsions may be followed by irregular muscular weakness or paralysis, the pattern depending on which part of the brain or spinal cord is most seriously involved. The mortality is 10 to 50 per cent, and residual symptoms are rare in recovered cases. Fortunately, the disease is not common.

Pathologic Lesions.—The outstanding change is extensive perivascular demyelination in the brain and cord. Globules of degenerated myelin and stainable free fat are taken up by macrophages. Petechial hemorrhages are often con-



Fig. 211.—Measles encephalitis, showing a focal area of demyelination of the type often seen in postinfection encephalitis.

spicuous. There is some perivascular cuffing with lymphocytes, but little or no evidence of ganglion cell destruction. Inflammatory cells are not seen in the areas of demyelinization. Thus the entire picture is quite different from that of the recognized viral infections, and in some respects appears more like that caused by vitamin deficiencies. The areas of demyelinization may be recognized in hematoxylin-eosin stained sections by their pale vacuolated appearance, but are brought out more clearly by special stains such as the Weigert stain.

Hemorrhagic encephalitis is a term applied to cerebral lesions characterized by many areas of hemorrhage ranging from less than a millimeter up to 3 or 4 mm. in diameter. The secondary type is caused by metallic poisons, such as arsenic and lead, and at times by known viruses, in which case it represents only an exaggeration of the normal tendency for perivascular hemorrhage to occur in viral encephalitis.

DIAGNOSIS OF VIRAL ENCEPHALITIDES

The clinical diagnosis of the various types of viral infection of the nervous system is usually impossible. During epidemics the laws of chance favor a diagnosis of the prevailing type. Toxic encephalitis, including the types caused by the heavy metals, also must be considered at times in the differential diagnosis.

Positive diagnosis in an individual case may be established by isolation of the virus, but unfortunately the viruses of lymphocytic choriomeningitis, herpes, mumps, lymphogranuloma venereum, Russian spring-summer encephalitis, and Venezuelan equine encephalitis are the only ones which can be isolated from spinal fluid with any degree of regularity. In all other types, brain or cord tissue obtained post mortem is necessary. Having established a strain of virus in mice, guinea pigs, or other laboratory animals, crossed immunity tests with known strains are carried out.

Diagnosis may be established also by the protection test, which is a test for the presence of neutralizing antibodies in the blood. Blood serum from the patient is mixed with viruses of known types, and injected into animals. If such animals are protected against St. Louis encephalitis, for example, while the control animals react positively, a diagnosis of this disease may be justified. This test is not positive until several days after the onset of the disease. The agglutination of virus-coated particles by patients' serum has also been used as a diagnostic measure.

Complement fixation tests are also available. In all of these immunologic tests carried out with patient's blood, the possibility of the existence of immunity before the current illness must be considered. A rise in titer of these tests during the course of the disease and convalescence establishes the diagnosis with a high degree of certainty.

Viral Diseases of the Respiratory System

Viral diseases with conspicuous involvement in the respiratory system in-

clude influenza, the common cold, psittacosis, "inclusion disease" (caused by the salivary gland virus), Adams' disease, Goodpasture's disease, and giant cell pneumonia. The four types mentioned last occur largely in infants and children. It is probable that other types of viral pneumonia occur without recognition.

General Considerations.—The lung, like the central nervous system, reacts to viral infections in a rather characteristic manner, so that the viral etiology of a pulmonary lesion may be strongly suspected from histologic evidence alone. Viral pneumonias are of the interstitial type. Inflammatory cells are largely of the mononuclear variety, and accumulate chiefly in the alveolar walls and in the peribronchial and septal connective tissue. The alveolar lining cells often undergo cuboidal metaplasia, and mitotic figures are seen in them. The alveoli either remain free from exudate or contain a serous or gelatinous exudate, with only a few inflammatory cells, chiefly mononuclears. Condensation of this exudate by inspired air often forms a hyaline eosinophilic membrane which lines the alveoli. These features, though suggestive, are not pathognomonic of the viral infection since they occur in infections with other intracellular parasites (Rickettsiae and Toxoplasma) and probably in certain bacterial and allergic inflammations of the lung.

The damage inflicted by viruses often makes the lung susceptible to bacterial invasion. Secondary bacterial pneumonia, with its usual picture of exudation into the air spaces, is often present in fatal cases, and may obscure the characteristic picture of the original viral pneumonia. There is evidence, for example, that a preceding infection of the lung with influenza virus is of etiological importance in certain epidemics of staphylococcal pneumonia.

The high morbidity rate of influenza and the common cold is explainable on the basis of their epidemiology. Droplet infection by sneezing and coughing is a mechanism well suited for the rapid and direct transfer of live virus from the respiratory mucosa of one individual to that of another. During epidemics it is probable that nearly all nonimmune members of a population acquire these diseases in mild or severe form.

INFLUENZA

Influenza occurs in endemic, epidemic, and pandemic forms. The conditions under which epidemics and pandemics occur are not clear.¹⁰⁴ During the last pandemic, which occurred during and following World War I (1918-1919), it is estimated that five hundred million cases occurred, with fifteen million deaths.

Etiology.—The etiology of influenza was extensively studied during the pandemic of 1918 and 1919, but no definite conclusion was reached. The influenza bacillus (*Hemophilus influenzae*) was often isolated but has been practically abandoned as the underlying cause of the disease. It is still regarded, however, as an important secondary invader.

In 1933, Smith, Andrewes and Laidlaw¹⁰⁵ reproduced the disease in ferrets by the intranasal injection of filtered nasal and throat washings from human patients. This experiment has been repeated successfully many times since then, and the viral etiology of influenza is widely accepted. Mice may also be infected by intranasal injection.¹⁰⁶ The disease produced in this way has a high mortality in mice, and pathologically one finds a pneumonitis of the interstitial type, with escape of many red blood cells into the alveoli. Several antigenically different strains, including type A and type B, may be identified by the complement fixation test and by the neutralization tests. The latter test is performed by mixing the unknown virus before injection with immune sera containing antibodies of known types. The virus is readily cultivated in fertile eggs, and has been studied extensively.

In spite of the demonstrated viral etiology of influenza, secondary or even simultaneous bacterial infection is important as a cause of death. The viral disease by itself is rarely fatal. In addition to *H. influenzae*, streptococci, staphylococci, and pneumococci are the most common bacterial invaders.^{107, 108}

Clinical Picture and Diagnosis.—The disease is characterized by sudden onset, with fever, sore throat, prostration, headache, and muscular pains. In uncomplicated cases, the illness lasts only a few days, but if pneumonia occurs the duration is longer. In sporadic and mild cases, differential diagnosis from the common cold may be difficult. It is possible to make an accurate diagnosis by the demonstration of neutralizing antibodies in the blood. The simplest way to do this is to make use of the fact, demonstrated by Hirst,¹⁰⁹ that influenza virus causes normal adult chicken erythrocytes to agglutinate. If the patient's blood contains antibodies, it will, when mixed with influenza virus, prevent the agglutination of red cells which takes place normally when virus is added to them. If strains of the A and B types are available, a differential diagnosis may be made in this way. Virus isolation in the fertile egg is a relatively simple procedure.

Pathologic Lesions.—There is acute inflammation of the nasopharynx, larynx,

trachea, and bronchioles. The mucosa of the trachea and bronchioles is deep red and swollen and may show small areas of superficial ulceration. The gross picture in the lungs is variable, depending on the type and severity of the secondary bacterial infection. In the less common uncomplicated cases, the lungs are deep red and firm in large or small circumscribed areas. Interstitial emphysema is common, and bubbles of air ranging up to 2 or 3 cm. in diameter are found in the interstitial tissue, subpleural tissue, and at times extending into the mediastinal tissue and even into the subcutaneous tissues of the neck. If lobar pneumonia has occurred, the typical picture of red or gray hepatization may be seen. In other cases the picture is indistinguishable from that of ordinary bronchopneumonia. Infection with hemolytic streptococci or *H. influenzae* often results in a diffuse hemorrhagic type of consolidation. In certain cases, particularly in children, with better resistance, the influenza bacillus causes discrete nodule formation grossly simulating miliary tuberculosis. (This picture is seen also in pneumonias caused by the influenza bacillus without preceding viral infection.) Staphylococcal pneumonia, with abscess formation, may occur at times as a complication of influenza.¹¹⁰

Microscopically, also, the picture is variable. In certain cases with early fatal termination a picture resembling that seen in experimental animals is found. The alveoli contain a fluid exudate with only a few red cells and neutrophiles, and a prominent hyaline membrane lining many of the alveoli. This hyaline membrane, which apparently is formed by the compressing action of air on the exudate, is seen in other types of viral pneumonitis. In most cases, this early picture is largely obliterated by superimposed bacterial pneumonia of the types seen without known antecedent viral infection. In the diffuse nodular type of lesion, the nodules are seen to be composed of peribronchiolar collections of inflammatory cells, with some connective tissue proliferation, and some exudate in the surrounding alveoli.

Changes in the viscera are less characteristic, and in general are those seen in any type of bacterial pneumonia or in any other acute infection. Complications include endocarditis and meningitis caused

by the influenza bacillus and empyema. Organized pneumonia, leaving one or more lobes permanently fibrous, was rather common during the pandemic of 1918 to 1919. Inclusions have not been found in association with the influenza virus.

Immunologic Aspects.—Successful vaccination is difficult because of the transient nature of the immunity produced and because of the existence of antigenically variant strains of the virus. Present evidence, however, suggests that the vaccine made from infected fertile eggs may produce fairly satisfactory immunity in man which lasts for several months. It is necessary, however, to use antigenically homologous strains in preparing the vaccine.

COMMON COLD

The common cold, or coryza, is probably the most important cause of disability among healthy individuals. Factors responsible for the high morbidity rate in this infection are its rapid and direct transmission by droplet infection, its short incubation period, the transient nature of the immunity developed, and the free intermingling of infected and noninfected individuals.

Etiology.—Upper respiratory infections form a confusing group from the point of view of accurate diagnosis. Clinically there is considerable overlapping between the common cold, influenza, and certain allergic and chemical inflammations of the respiratory tract. The almost constant occurrence of secondary bacterial infection in association with the common cold, leading to pharyngitis, sinusitis, laryngitis, and bronchitis, as well as rhinitis, introduces further confusion into the picture.

Dochez and his co-workers¹¹¹ were able to transmit a characteristic upper respiratory infection to chimpanzees and human volunteers with filtered nasal washings from about 50 per cent of patients suffering from the picture of the common cold. For this reason it is generally accepted that many colds are primarily of viral etiology. It is possible that a number of immunologically distinct viruses may be involved. The factors which determine the variable severity and localization of associated streptococcal and other bacterial infections are not known. There is some evidence that allergy may play a part in the etiology of the common cold, but the use of antihistaminic drugs has not been attended by significant results. The virus of the common cold has probably been cultivated in fertile eggs.

Pathologic Lesions.—In the early stages one finds hyperemia and edema of the involved mucus membranes, with a clear serous exudation. Later, with the advent of bacterial infection, the exudate becomes mucopurulent, and the picture is

a typical example of the catarrhal type of inflammation. Hyperplasia of the mucus glands occurs, and increased mucous secretion may persist for weeks or months after recovery. Involvement of the mucous membranes of the accessory nasal sinuses is of common occurrence, and this sinusitis may prolong the infection because of the imperfect drainage of these cavities. No definite inclusion bodies have been found in connection with the common cold.

PSITTACOSIS AND ORNITHOSIS

Psittacosis is acquired by inhalation of the virus in dried urine and feces from infected psittacine birds.¹¹² It has been shown that several birds other than those of the parrot family, including pigeons, chickens, and the fulmar petrel (a sea gull) may harbor a similar virus which causes human infection. Infection with this virus is known as ornithosis.¹¹³ Latently infected birds, without clinical evidence of illness, are known to be a source of danger.

Clinically, psittacosis is an acute febrile illness, with intense headache, and physical signs of an atypical pneumonia. Leukopenia, instead of the leukocytosis which accompanies bacterial pneu-

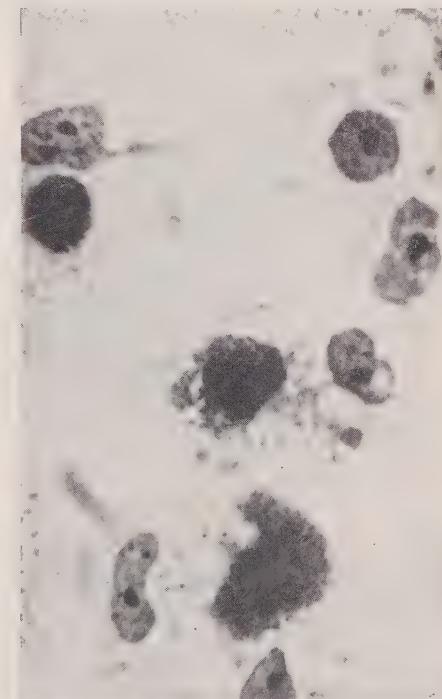


Fig. 212.—Psittacosis. Three deeply stained granular cytoplasmic inclusions composed of closely packed but discrete elementary bodies are seen. (From a tissue culture preparation.) (From Anderson, Synopsis of Pathology.)

monia, is an important diagnostic feature. The mortality in some outbreaks has been as high as 40 per cent. In cases from which ornithosis virus is isolated, the mortality is usually very low.

Pathologically, one finds splenomegaly, and congestion and cloudy swelling of the viscera. Small focal necroses may be visible on close inspection in the liver and spleen. Microscopically these areas contain many mononuclear cells. The most characteristic changes are in the lungs. Here we find patchy or confluent pneumonic consolidation. Microscopically the picture is that of a viral pneumonia as distinguished from that of bacterial pneumonia.¹¹⁵ Mononuclears, rather than neutrophiles, predominate, and the alveolar walls are thickened by the accumulation of these inflammatory cells. The alveolar lining cells are stimulated and become cuboidal in type with frequent mitoses. The alveoli contain a rather gelatinous exudate, containing relatively few cells, the majority of which are mononuclears. The brain shows congestion and edema, and petechial hemorrhages may be present.

Etiological Agent.—Spherical clusters of minute coccoid elementary bodies of rather characteristic appearance¹¹⁶ are found with great difficulty in sections of human lungs, but are very conspicuous in the brains of mice following intracerebral injection of the virus (Fig. 212). The virus is of relatively large size (0.275 micron in smallest diameter). It has been cultivated in fertile eggs. The elementary bodies of the virus are rather similar to rickettsiae, and have been included with these organisms by some workers. They are usually excluded from this group, however, in view of the fact that they have not been found in insects.

The laboratory diagnosis of psittacosis or ornithosis is made either by isolating the virus from sputum or throat washings or by demonstrating the presence of complement-fixing antibodies. Mice are the most convenient animals for the isolation of the virus, and should be injected intracranially as well as intraperitoneally and intranasally, since certain strains of the virus appear to be primarily neurotropic in the mouse.¹¹⁷

Lymphogranuloma venereum, which is associated with rather similar elementary bodies, is closely related immunologically to psittacosis, although clinically it is an entirely different disease (see page 291).

VIRAL PNEUMONIAS OF INFANTS AND CHILDREN

Several types of inclusions have been described in the lungs of infants and children in association with pneumonia. In none of these diseases, however, has a virus been isolated.

A type of epidemic pneumonia in infants, with a mortality of about 20 per cent, has been described by Adams.¹¹⁸ The pathologic picture in the lungs is that of an interstitial pneumonitis, suggestive of the action of a virus, and medium-sized, spherical, eosinophilic cytoplasmic inclusions are found in the bronchial epithelium. Nuclear inclusions are not found. Although at-

tempts to isolate a virus have been unsuccessful, the morphologic evidence strongly suggests a viral etiology for this disease.

Goodpasture and his co-workers¹¹⁹ have described nuclear inclusions filling but not distending the nuclei of bronchial epithelial cells, in association with pneumonia in infants. These inclusions closely resemble those of herpes simplex. Similar inclusions are seen in the lungs in an occasional case of bronchopneumonia in adults, but virus isolation has not been achieved.

The salivary gland virus may cause clinically important or fatal lesions in many organs (see page 335). Occasionally both in infants and adults, the huge bizarre inclusions characteristic of the presence of this virus may be present in great numbers in association with extensive inflammatory consolidation of the lungs.

Giant cell pneumonia, first described by Hecht in 1910, is a rare but distinctive pneumonia of infancy and childhood. It is an interstitial pneumonitis, the most important diagnostic feature being the formation of large multinucleated giant cells by proliferation and fusion of cells which line alveoli, alveolar ducts, and bronchioles. Cytoplasmic inclusions, pleomorphic and often very large, are found in these cells, and also less numerous small nuclear inclusions.¹²⁰ A similar histologic picture, with giant cells and similar inclusions, is found in fatal early uncomplicated measles, and in canine distemper in animals. Present evidence, which is entirely morphologic in nature, suggests that giant cell pneumonia is a viral disease. Its occurrence in measles may mean that it is an atypical response to the measles virus, or to some virus associated with that of measles.

PRIMARY ATYPICAL PNEUMONIA

This is an epidemic disease, with very low mortality, occurring chiefly in young adults living under the conditions of institutional or military life. It has been of frequent occurrence in army camps. Clinically it is characterized by coryza, fever, sore throat, headache, and a dry cough with little sputum. Leukopenia, rather than the leukocytosis which accompanies bacterial pneumonia, is the rule. Typable pneumococci are not found in the sputum. Roentgenograms show consolidation of the lung, spreading outward from the hilus.

Grossly, the lungs show patchy, deep red, firm consolidation. Microscopically, the changes described above as characteristic of viral pneumonia are seen.^{121, 122} The etiology of this condition is unknown. Strains of psittacosis or ornithosis virus have been recovered occasionally (page 325), but many attempts to isolate a virus have been unsuccessful. Recent evidence incriminating *Rickettsia burneti* as the

etiological agent of such outbreaks has been discussed (page 306). The term "virus pneumonia" has been applied to the condition, but "atypical pneumonia" seems preferable at the present time since evidence of the viral etiology of the majority of cases is lacking.

Diagnosis may be difficult, but in addition to the clinical features mentioned above, the presence of cold hemagglutinins¹²³ in increasing titer, the failure to respond to penicillin, and failure to elicit immunologic evidence of ornithosis, Q fever, lymphocytic choriomeningitis, toxo-



Fig. 213.—Cytoplasmic inclusions in multinucleated cells lining pulmonary alveoli. Several faintly stained nuclear inclusions are also present (from a case of giant cell pneumonia). (From Anderson, Synopsis of Pathology.)

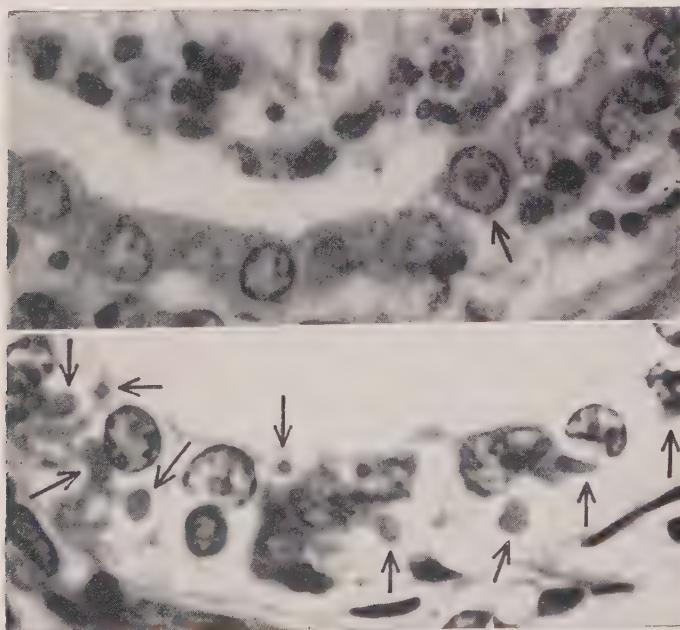


Fig. 214.—A nuclear inclusion (above) and several cytoplasmic inclusions (below) (giant cell pneumonia). (From Anderson, Synopsis of Pathology.)

plasmosis, or histoplasmosis are all helpful. These immunologic tests are not generally available for routine use, and the etiological identification of outbreaks of atypical pneumonia is largely a research procedure.

Cutaneous Viral Infections

SMALLPOX (VARIOLA)

Smallpox is a highly contagious viral disease, characterized by fever and other evidence of severe generalized infection, followed after a few days by a characteristic cutaneous eruption. The cutaneous lesions occur in single crops. Beginning as macules, they become papules, then vesicles, and finally pustules, the process of evolution extending over a period of about ten days. Three types are recognized: discrete,



Fig. 215.—Smallpox in an unvaccinated woman. (Courtesy Dr. Samuel Sweitzer. From Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Co.)

confluent, and hemorrhagic, with increasing mortality in the order mentioned. A mild form of the disease, with a mortality of about 1 per cent is recognized, and has been called *alastrim* or *parasmallpox*. The term *varioloid* is applied to infections modified by vaccination, in which constitutional symptoms are mild and the cutaneous lesions discrete and often small, omitting the pustular stage. Vaccination has brought the disease under control in most countries,^{124, 125} and only about 1,000 cases per year have been reported in this country in recent years. In other countries, notably India, West Africa, and South America, the morbidity and mortality rates are much higher.

Pathologic Lesions.—The cutaneous lesions in the papular stage have a diameter of 2 to 4 mm. and are partially buried in the skin. The fluid which accumulates to form the vesicles is at first clear, but soon becomes cloudy, and eventually purulent. The pustules then become umbilicated (Fig. 215), and in the process of desiccation a small dry "seed," rich in virus, is extruded.

The stage of pustule formation corresponds to bacterial invasion, usually by streptococci or staphylococci. The blood culture is positive for these organisms, and they are undoubtedly an important cause of mortality in the disease. Healing often results in the formation of depressed scars (pitting) particularly in the confluent form of the disease.

In the hemorrhagic form of the disease there is extensive hemorrhage into and around the cutaneous lesions, and often also into the corium, an occurrence which gives a particularly bad prognosis. Hemorrhage may occur also into the pelvis of the kidneys and into the lungs, giving a type of hemorrhagic pneumonia.

Microscopically, the cutaneous lesions first show vascular congestion and mononuclear cell infiltration. The etiological agent invades the epithelial cells, causing them to swell and eventually to become necrotic. In the vesicular stage fluid escapes between the epithelial cells. Previous to the occurrence of necrosis, inclusion bodies known as Guarnieri bodies are found in the epithelial cells (Fig. 216, C). These are composed of spherical elementary bodies, the Paschen bodies, which are generally accepted as the cause of the disease, and which Goodpasture has named *Borrelia variolae hominis*.⁴⁸ Intranuclear inclusions also have been described, but these do not appear to be composed of elementary bodies, and their exact nature is not clear. Neutrophiles become prominent in the necrotic stage of the lesion, and even more numerous with the advent of bacterial infection.

On the mucosal surfaces of the nasopharynx, larynx, trachea, esophagus, and vagina, similar lesions are initiated, but because of the absence of a horny layer these lesions often become punched-out ulcers rather than pustules.

In fatal cases, pneumonia is often present. Although it is difficult to follow the sequences, there is evidence that the pneumonia is primarily of the interstitial or viral type, which is obscured later by superimposed streptococcal and other bacterial infections. The pneumonia is often hemorrhagic in type. In septicemic cases, acute splenic tumor and abscesses in the kidneys may be found, and bacterial endocarditis is occasionally seen. The bone marrow may show hemorrhages and a relative absence of neutrophiles. Leukopenia is a characteristic finding, and the relative absence of granulocytes may be an important factor in the development of bacterial infection.

Vaccinia or cowpox virus resembles that of smallpox morphologically and immunologically, and the histological changes in the skin at the site of vaccination are essentially identical with those of smallpox. Nuclear inclusions, however, are not seen. Generalized cutaneous lesions occasionally occur, particularly in infants with eczema who come in contact with the virus.¹²⁶

CHICKEN POX (VARICELLA)

Chicken pox is a mild communicable disease of childhood, with a characteristic cutaneous eruption. It may be associated with coryza and slight fever, but generalized symptoms often are absent. It spreads rapidly among children, either by direct contact or by droplet infection. Severe cases may be complicated by postinfection encephalitis. In the absence of complications, which are not common, the mortality is almost zero.

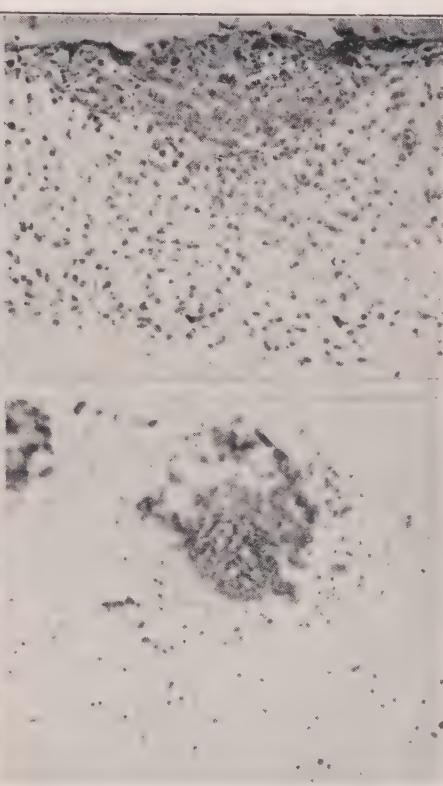
epidermis. Many of the epidermal cells contain homogeneous or finely granular eosinophilic nuclear inclusions which somewhat resemble those of herpes simplex, and similar inclusions are sometimes found also in the cytoplasm. Healing of the cutaneous lesions occurs by discharge of the fluid with the formation of crusts which eventually drop off.

In the rare cases which apparently die of uncomplicated viral infection, cytologic changes similar to those occurring in the skin are found

A.



B.



C.



D.

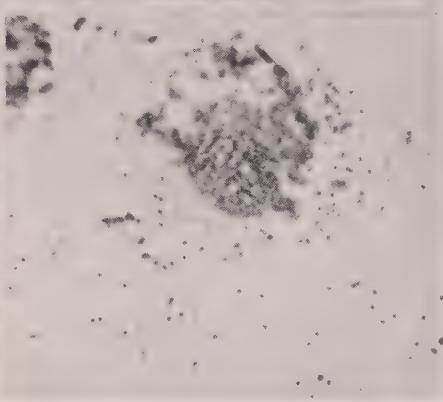


Fig. 216.—Cultivation and demonstration of virus of smallpox. (Courtesy Dr. G. J. Buddingh: Am. J. Hyg. 28: 130, 1938.)

A, Chorioallantois of chick embryo, actual size, showing gross alteration produced by inoculation with variola 72 hours previously. The unfixed, fresh specimen in dark-field photograph.

B, Inflammation of epithelium of chorioallantois sectioned 72 hours after infection, showing proliferation and vesicle formation. ($\times 225$)

C, Guarnieri bodies as seen by high magnification of tissues shown in B. ($\times 1400$.)

D, Paschen bodies seen in and about the smear of an infected epithelial cell, in a 72-hour lesion. (Smear prepared by the Morosow technique.)

Pathologic Lesions.—In the great majority of cases, the cutaneous eruption is the only lesion seen. The lesions are most numerous on the face and trunk, but eventually may have a generalized distribution, often including the buccal and pharyngeal mucosa.

Microscopically there is congestion and edema of the corium and infiltration with mononuclear cells. Vesicles containing fluid are found in the

in the epithelial cells of the esophagus, pancreas, liver, adrenals, renal pelvis, and bladder.¹²⁹ Typical viral pneumonitis with characteristic nuclear inclusions has also been described.¹³⁰

Complications.—Complications, usually of a mild nature, occur in about 5 per cent of all cases of chicken pox.¹³¹ These include otitis media, abscess formation, suppurative lymphadenitis, gangrene of the skin, nephritis, and

encephalitis of the postinfection type. The mortality is less than 0.4 per cent.

Etiological Agent.—The virus of chicken pox is relatively large, estimates varying between 145 and 250 millimicra. Epidemiologic evidence suggests that it is closely related to that of herpes zoster, and there is some immunologic evidence to support this belief. The exact relationship of these two viruses is not yet entirely clear.¹³²

MEASLES (RUBEOLA)

Measles is a highly communicable disease, characterized by fever, cough, coryza, conjunctivitis, and an erythematous cutaneous eruption of characteristic appearance. Although in itself a mild disease, it lowers resistance to other infections. The rash, which is composed of small reddish maculopapules, appears first on the face and spreads rapidly to the abdomen and extremities. Koplik spots, which are most important from a diagnostic point of view, represent the first manifestation of the eruption, and usually appear opposite the molar teeth, at times involving a large area on the lateral buccal mucosa. They consist of minute white flecks, formed by necrotic epithelial cells, and each lesion is surrounded by a red areola. They often appear two or three days before the cutaneous eruption become visible. Koplik spots have been described in fatal cases in the intestinal mucosa.

theelial cells show intracytoplasmic vacuoles and in the later stages, hyaline degeneration and necrosis. Rounded hyaline bodies resembling inclusions have been described, but these are inconstant and are not usually accepted as characteristic of the activity of a virus. Vascular thrombosis and extravasation of erythrocytes is rarely seen.

The Koplik spots show a picture in general like that of the cutaneous lesions, but with more marked necrosis of epithelial cells and the consequent accumulation of greater numbers of neutrophiles. Irregular ulceration of the buccal mucosa may occur. On the conjunctivae and in the pharynx, larynx, trachea, and bronchi, there is mucopurulent exudation and intense vascular congestion.

Bronchopneumonia, which is the most common fatal complication, is usually studied post mortem two or three weeks after the onset of the disease. In such cases, it may be interstitial in type, but is usually of bacterial nature, not differing from the pneumonia which may follow influenza or which may occur without antecedent viral infection. Hemolytic streptococci are often isolated from the lung.

A curious feature of the pathology of measles is the occurrence of giant cells in the tonsils and lymph nodes,¹³⁴ and in the lymphoid tissue of the appendix. These giant cells have many closely packed hyperchromatic nuclei. They are present in the prodromal stages, and appendectomy may lead to a diagnosis of measles several days before the characteristic clinical features have appeared. The relationship of these giant cells to those seen in giant cell pneumonia, which often is associated with measles, is uncertain (see page 326).

Encephalitis is occasionally seen as a complication of measles. Although the virus of measles has been isolated from the brain in such cases post mortem, the histologic features are like those of other types of postinfection encephalitis (see page 322).

Etiological Agent.—Measles is accepted as a viral disease, but our knowledge of the virus is incomplete. Transmission has been achieved only to human volunteers, to rhesus monkeys, and to fertile eggs. It is of interest that giant cell formation in lymphoid tissue is found in monkeys, as well as in man.¹³⁵ Certain observers have postulated that two distinct viruses may be involved in the etiology of measles.

Complications.—In addition to bronchopneumonia, which is the usual cause of death, and encephalitis, which has been discussed, a variety of bacterial complications should be mentioned. These include otitis media, cervical adenitis, gangrenous stomatitis, endocarditis, and tuberculosis. The latter disease may appear as an exacerbation of a previously latent infection, as a result of lowered resistance.

RUBELLA (GERMAN MEASLES)

Rubella is a mild self-limited disease with slight fever, malaise, enlargement of the mastoid, occipital, and posterior cervical lymph nodes, leukopenia with relative lymphocytosis, and a mild generalized macular eruption. There is evidence that the disease may be entirely



Fig. 217.—Giant cells with closely packed nuclei in lymphoid tissue of appendix removed in the prodromal stage of measles.

Pathologic Lesions.—The cutaneous lesions, studied by biopsy, show vascular congestion and edema of the corium, with perivascular accumulations of lymphocytes and macrophages. The capillary endothelial cells are swollen and often show mitotic division. There is hyperkeratosis, particularly in the later stages, and the epi-

asymptomatic, and detectable only by leukopenia and lymph node enlargement in children known to have been exposed. In some cases there is coryza. The disease is most common in children, but many individuals are first exposed and infected as adults.

There can be little doubt concerning the viral etiology of rubella, although the disease has not been extensively studied from this viewpoint.

It has been shown recently that the occurrence of rubella during pregnancy may cause serious congenital defects in infants,¹³⁷ including congenital heart lesions, microcephaly, mental retardation, deaf-mutism, dental defects, and cataract. It is apparent that the virus of rubella deserves thorough study, with a view to the development of methods of immunization during childhood.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a benign skin disease, characterized by the occurrence of raised, umbilicated, waxy cutaneous nodules. These lesions may be multiple, in which case the diagnosis is usually made clinically, or single, in which case the lesion may be suspected of being neoplastic and is often excised for diagnosis. The lesions heal spontaneously, usually after a few months, and are not associated with constitutional symptoms. The prickle cells of the epidermis undergo degeneration, with the development of rounded hyaline masses (*molluscum bodies*) in their cytoplasm. These eosinophilic inclusion bodies are aggregations of the minute elementary bodies of the virus.

Because of their similarity to the elementary bodies of smallpox, vaccinia, and cowpox, Goodpasture¹³⁸ has named them *Borrelia mollusci*. Except for the occurrence of the molluscum bodies and the umbilicated nature of the lesion, the histologic picture resembles that of a benign papilloma of the skin. (See Plate IV, facing next page.)

HERPES SIMPLEX

Herpes simplex is the common "cold sore" or "fever blister" which occurs most often on the lips, but is also seen on the buccal mucosa (herpetic stomatitis), on the genital mucosa, on the conjunctiva, and on the skin of the face or other regions. The herpes virus has been isolated from a type of eczema in infants (eczema herpeticum). The common lesion or cold sore occurs not uncommonly in school children, where it is spread by direct contact, as by kissing. Constitutional symptoms are infrequent. Most characteristically, the lesions occur in the course of some febrile illness. Apparently latent infection is common, and the virus is stimulated to produce characteristic lesions by some unknown mechanism which commonly acts in the presence of fever. It has occurred often during artificial fever therapy.¹³⁹ In rabbits, latent infection is aroused to activity by anaphylactic shock.

Pathologic Lesions.—The lesions are at first erythematous, but rapidly assume their characteristic form of clusters of small superficial blisters containing clear fluid. Histologic study shows edema and congestion of the corium,

vesicle formation, and infiltration of many neutrophiles in the corium and into the epidermis around the vesicles. The epidermal cells show hyperplasia and necrosis. In the stage preceding necrosis, large eosinophilic nuclear inclusions are seen, which often fill but do not distend the nuclei. There is condensation and margination of the nuclear chromatin, so that the nucleus is represented by an irregular black margin, surrounding the inclusion, but often separated from it by a clear zone. Certain observers have described bacillary elementary bodies. In any case, the inclusions are definitely granular when suitably stained, and the relatively large size of the virus would suggest that elementary bodies might be visible.

If vesicle fluid from a human lesion is rubbed into the scarified cornea of a rabbit, a specific viral conjunctivitis, with many nuclear inclusions of the type already described, is produced.¹⁴⁰ The virus also causes a serially transmissible encephalitis in mice.

Relation to Encephalitis in Man.—The histologic resemblance of herpes encephalitis in mice to human encephalitis of the Economo type, together with the occasional recovery of herpes virus from normal human brain tissue, has suggested the possibility that the herpes virus may be the cause of lethargic (Economo) encephalitis. Against this view is the almost uniform absence of characteristic inclusions in the latter disease, and the failure (with a few possible exceptions) to recover the herpes virus from the brain. In rare cases of human encephalitis, typical nuclear inclusions are found, and the herpes virus has been recovered in such cases.⁹⁸ These cases probably are to be regarded as herpes encephalitis, unrelated to lethargic encephalitis (see page 319). It also is probable that a type of chronic encephalitis may be caused by the herpes virus (see page 316).

Hepatoadrenal Necrosis.—This disease has been reported infrequently, and diagnosis has been made only as a result of postmortem study. It occurs only in young infants, and the clinical picture is vague. The important pathologic lesions are extensive focal necrosis in the liver and adrenals, the individual lesions in the liver ranging up to 4 mm. in diameter. Microscopically, the hepatic and adrenal epithelial cells, particularly at the edges of the necrotic areas, contain nuclear inclusions, which, as pointed out by Hass in his original description of the condition, closely resemble those of herpes simplex.¹⁴¹ The condition probably is visceral herpetic infection without cutaneous involvement. This view is supported by the isolation of the herpes simplex virus from several cases.^{142, 142a} Inconspicuous herpetic lesions of the genital tract in parturient women are associated with fatal generalized neonatal infection.^{142a}

HERPES ZOSTER

Herpes zoster, commonly known as shingles, is characterized by the formation of an erythematous and vesicular eruption along the course of sensory nerves. The lesions occur most often on the trunk or face, and are usually associated with pain, discomfort, fever, and malaise. With rare exceptions, the lesions are unilateral; on

the face, for example, they rarely cross the midline. Serious ocular involvement may occur.

Pathologic Lesions.—The skin lesions show inflammatory changes in the corium and degenerative changes in the epidermis which resemble those seen in herpes simplex. The characteristic features, however, are edematous "ballooning" of the epidermal cells, with the formation of giant cells by amitotic division, and the presence of nuclear and at times also of cytoplasmic inclusion bodies.¹⁴⁴ These inclusions are identical with those seen in chicken pox, and the nuclear forms differ from those of herpes simplex in that they fill the nuclei less completely than the latter.

In contrast to herpes simplex there are in herpes zoster striking changes in the ganglia of the posterior root nerves and in the cerebral ganglia. These consist of degenerative changes in ganglion cells with neuronophagia, vascular congestion, and perivascular cuffing. The lesion has been characterized as the sensory analogue of poliomyelitis. In the process of repair, small or large areas in the ganglia may be converted into scar tissue. The lumbar and sacral nerves and the anterior branch of the trigeminal nerve are most often involved. An increased cell count in the spinal fluid is often found.

The above-described changes are usually regarded as the basic lesion in herpes zoster. Inclusions bodies, however, which are the only available evidence of the actual presence of the virus, are not found in the ganglia, but are numerous in the epidermal cells.

Miscellaneous Viral Diseases

MUMPS

The virus of mumps, or epidemic parotitis, has an affinity for the salivary glands and for the gonads, but causes lesions also in the pancreas, thymus, thyroid, central nervous system,⁵ and in Bartholin's glands and the lacrymal glands. It is most common between the ages of 5 and 15 years. The virus is present in the saliva, and transmission is by close contact or droplet infection. The incidence of the disease is much lower than that of measles and only a relatively small proportion of exposed individuals show clinical evidence of infection. The virus, which is of medium size, multiplies in fertile eggs, and causes parotitis in monkeys when injected via Stenson's duct.

Pathologic Lesions.—Because of the very low fatality rate, the pathologic lesions in man have been incompletely studied. It is reasonable to assume, however, that they are identical with the lesions produced experimentally in monkeys.¹⁴⁶ In the latter, the salivary glands are swollen and edematous, and small capsular hemorrhages are often seen. There is interstitial serofibrinous exudation, catarrhal exudation into the excretory ducts, and disintegration of the acinar cells. The cellular exudation is composed chiefly of mononuclear cells. Healing occurs by epithelial regeneration.

In the orchitis of human beings necrosis of tubular epithelium is seen in focal areas, and many tubules become distended with purulent

exudate. Healing may be associated with some testicular atrophy, but impotence and sterility are of rare occurrence, partly because the lesion is often unilateral, but also because of the patchy distribution of the tubular necrosis. The spleen is palpably enlarged in about 20 per cent of cases, and the pancreas may be sufficiently swollen to be felt manually. The pancreatic lesion is probably hemorrhagic in nature.

In cases of clinically evident meningoencephalitis, the spinal fluid is under pressure and usually clear, although it may contain as many as 1,200 lymphocytes per cubic millimeter. There is some evidence that the virus of mumps is the actual cause of the lesion in the central nervous system. Deaf-mutism is an uncommon complication of mumps, and has been variously ascribed to inflammation of the labyrinth and to involvement of the eighth nerve.

Clinical Pathologic Correlation.—As has been brought out, mumps is a rare cause of sterility. Pancreatitis is manifested by vomiting, diarrhea, and elevated serum amylase. The possible relation of pancreatitis caused by the virus of mumps to subsequent diabetes is debatable. Meningoencephalitis is indicated by drowsiness, and by reflex changes such as the Kernig and Brudzinski signs.

YELLOW FEVER

Yellow fever is an acute viral infection of great importance in the tropics, particularly in Africa and South America. It has disappeared from North America and Europe. The outstanding clinical features are fever, severe jaundice, hematemesis, hemorrhage into the gastrointestinal tract, and evidences of severe renal damage including hematuria and albuminuria. Anuria and uremia are common in fatal cases.

Epidemiology.—The transmission of the disease by a mosquito (*Aedes aegypti*) was established in 1900. This discovery led to the control of the disease and made possible the construction of the Panama Canal. Since yellow fever in man either terminates fatally or leads to recovery without persistence of the virus in the body, it was hoped that the screening of all infected individuals might cause the complete disappearance of the disease from the world. Unfortunately, it has been found that the man-mosquito-man cycle of infection does not represent the complete picture of the epidemiology of the disease. A reservoir of infection has been found in monkeys and perhaps exists in other wild jungle animals and there is evidence that insect vectors other than the *aegypti* mosquito may transmit the disease. The endemic form of the disease in South America has been called jungle yellow fever.¹⁴⁸ This disease is identical with the disease transmitted by *Aedes aegypti* in all respects except its epidemiology.

Pathologic Lesions.—Postmortem examination in fatal cases usually shows intense jaundice of the skin and conjunctivae, but in fulminant cases there may be only slight jaundice. Extravasated blood may be found in the nasopharynx, gums, and in the subcutaneous tissue. Hemorrhage into the stomach and intestines is common.



PLATE IV.—*Molluscum contagiosum*. The rounded, hyaline molluscum bodies occupy the superficial portion of the epidermis. *RB*, Transformation of epithelial cells into rounded bodies; *MB*, typical molluscum bodies. (From McCarthy, *Histopathology of Skin Diseases*, The C. V. Mosby Co.)

The outstanding lesions of yellow fever are seen in the liver.¹⁴⁹ Grossly, this organ is of about normal size, pale yellow, and greasy in consistency. There may be hemorrhagic areas, as in many other organs. Microscopically, there is extensive necrosis of liver cells in the midzonal area of the lobules (Fig. 218). Adjacent to the areas of necrotic liver cells are liver cells which are less severely damaged and which contain fat globules of large or small size. The necrotic liver cells are swollen, eosinophilic, and show a finely granular cytoplasm, in which areas of hyaline necrosis known as Councilman bodies may be seen. Inflammatory cell infiltration is not conspicuous.

fibrous tissue, but hepatic cirrhosis as a sequela of yellow fever has not been reported and there is evidence that it does not occur.

The kidneys are pale and swollen, with capsular tension, and often are somewhat bile stained. Microscopically they show severe degeneration of tubular epithelium, and microscopic areas of hemorrhage are often seen. The spleen is dark red and friable, and microscopically shows extreme congestion and endothelial hyperplasia. The heart is pale and flabby with scattered petechial hemorrhages in the pericardium. Microscopically there may be seen degeneration of the myocardial fibers in some cases.¹⁵⁰ Although the yellow fever virus causes

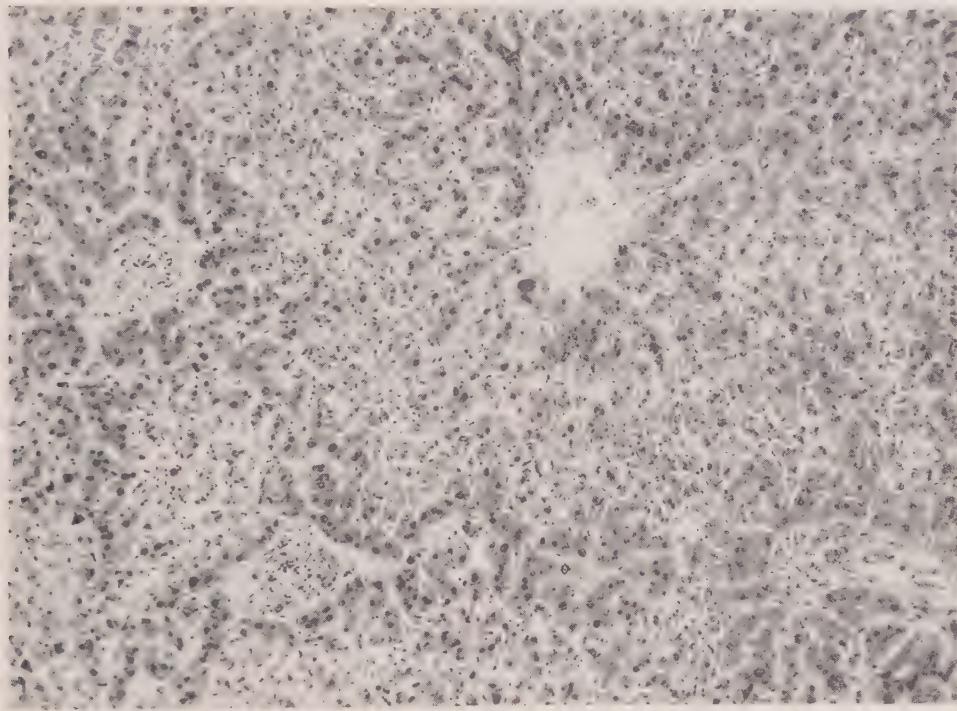


Fig. 218.—Yellow fever. Liver lesion is characterized by midzonal necrosis as shown above; however, the damage may involve other portions of the lobule or even the entire lobule. The early degeneration and necrosis of hepatic cells are attended by relatively little inflammatory reaction. (AFIP No. 68426. From Ash and Spitz, Pathology of Tropical Diseases, W. B. Saunders Co.)

Nuclear inclusions which are less prominent and more difficult to recognize than those of other viral infections are often found in human livers, and are almost constant in the hepatic cells of monkeys dying from yellow fever. This type of inclusion consists of a rather irregular eosinophilic mass adjacent to the nucleolus and often surrounding it in the form of a ring. Since similar inclusions may be found in liver cells in patients dying as a result of severe burns, their specificity is not absolute, and their relation to the elementary bodies of the virus is doubtful. Many liver cells are seen in mitotic division, even in the acute necrotizing stage of the lesion. The necrosis of liver cells is so extensive that one might expect repair by

encephalitis in the mouse, human brains show no lesions except congestion and petechial hemorrhages and rare foci of perivascular lymphocytic infiltration.

Human vaccination at the present time is carried out by injecting live virus which has been modified by cultivation in chick embryos in such a way that it has lost not only its "viscerotropic" but also its "neurotropic" properties.¹⁵¹

Laboratory diagnosis is made by animal inoculation (using mice or monkeys), by the protection test, or by microscopic examination of liver tissue removed post mortem. The protection test is carried out in mice and has been used not only for the diagnosis of individual cases but as a method of surveying a large area

for the presence of individuals who are immune to (and who therefore have recovered from) yellow fever. In individual cases of acute illness, diagnosis is based on a change in the protection test from negative to positive during the course of the illness, since a single positive test may mean only that the patient has had yellow fever in the past.

The microscopic picture described above in the liver is practically pathognomonic of yellow fever. For purposes of epidemiological study, therefore, the diagnosis may be made by examination of liver tissue removed by postmortem viscerotomy, without carrying out a complete autopsy. Such viscerotomy studies, which may be carried out by nonmedical assistants, have often shown the existence of yellow fever in areas where it was not previously known to occur.¹⁵²

TRACHOMA

Trachoma is a chronic progressive viral disease of the conjunctiva, with later invasion of the cornea, often leading eventually to partial or complete blindness. There is no evidence that animals other than man are naturally affected. In man, the disease is transmitted by direct contact with ocular secretions.

Etiological Agent.—Attempts to propagate the virus in fertile eggs or tissue cultures have been unsuccessful. The typical lesions of the disease have been produced in the eyes of monkeys by the direct transfer of filtered washings from an infected human eye. The virus is relatively large, and passes through filters with difficulty. In film preparations from the infected human conjunctiva, perinuclear clusters of coccoid elementary bodies are usually found in small to moderate numbers, and larger blue-staining "initial" bodies have also been described.^{154, 155}

These inclusions, which are called Halberstaedter-Prowazek bodies, are found in the conjunctival epithelial cells. They are somewhat similar to those seen in psittacosis and in lymphopatia venereum. All three viruses are relatively large, and show some therapeutic response to the sulfonamides, a fact which sets them somewhat apart from other viruses. A definite relationship between the presence of the trachoma inclusions and the infectivity of tissues has been demonstrated.

Pathologic Lesions.—The infected conjunctival epithelial cells show proliferation and eventual necrosis. The inflammatory cell response is primarily mononuclear, but, with secondary bacterial infection, neutrophiles appear. In the subepithelial tissues of the eye there is capillary congestion and many newly formed capillaries are seen. Follicles, or granular elevations, are often present on the conjunctiva. These follicles are composed of focal collections of lymphocytes and macrophages, with actual lymph follicle formation. The epithelium becomes hypertrophied and is thrown into folds. In the deeper tissues, scar tissue formation is evident. A picture similar to that of trachoma may be seen in eyes responding to other types of prolonged irritation, but diagnosis can be made on the

basis of the clinical picture and the presence of inclusions. (See also page 713 and Figs. 604, 605, and 606.)

In the cornea, there is epithelial proliferation, followed by desquamation and ulcer formation. Infiltration of mononuclear cells into the deeper layers of the cornea, vascularization, and scar tissue formation render the cornea opaque and lead to blindness.

Inclusion blenorhoea and *swimming pool conjunctivitis* are more benign types of viral conjunctivitis. Inclusions similar to those of trachoma are seen in smears from the conjunctiva, but follicle formation is less conspicuous and scarring does not occur. Recovery takes place without complications. These infections are transmissible to the eyes of monkeys. Their relation to each other and to trachoma are unknown, since immunity does not develop as a result of infection with any of these three viruses.

EPIDEMIC KERATOCONJUNCTIVITIS

Epidemic keratoconjunctivitis is a recently recognized viral infection which causes redness and swelling of the conjunctiva.¹⁵⁶ It has occurred in epidemic form among factory workers in several areas in the United States since its discovery in 1940. Mild systemic symptoms occur in the early stages of the infection, and severe headache may occur.

The etiological agent may be transmitted serially by intracerebral injection in mice. Neutralizing antibodies appear in the blood of infected humans, and the demonstration of such antibodies is a valuable aid in diagnosis. The virus apparently is closely related to that of St. Louis encephalitis.¹⁵⁷

The pathologic lesions have not been fully studied. Scrapings from the edematous and hyperemic conjunctiva show chiefly lymphocytes and macrophages in addition to epithelial cells. No inclusions have been described in association with this infection. There is some enlargement of the preauricular lymph nodes. Since fatalities do not occur, nothing is known of the systemic lesions.

After a course of from one to eight weeks the infection clears up, usually without residual damage to the eyes, but occasionally with some visual loss as a result of corneal opacity.

DENGUE

Dengue or breakbone fever is an acute mosquito-borne viral disease with a mortality of less than 1 per cent. It is characterized by severe pains in bones, muscles, and joints, fever, an erythematous or maculopapular skin eruption, severe prostration, and marked leukopenia. The disease is of economic importance in many parts of the world, including the southern United States. The general pathology of the disease is not known. Several strains have been adapted to mice, with loss of virulence but retention of immunizing properties for man.

PHLEBOTOMUS FEVER

Phlebotomus fever, or pappataci fever, resembles dengue clinically, but is transmitted by

the sand fly *Phlebotomus papatasii*. It occurs in the Mediterranean regions, Egypt, India, and China. As in the case of dengue, human volunteers are infected by the injection of filtered blood. As in dengue, there is marked leukopenia, but cutaneous eruption usually does not occur. Nothing is known concerning the general pathologic changes in uncomplicated cases.

VIRAL ENTERITIS

Although certain epidemics of infectious enteritis have long been suspected of having a viral etiology, there is little concrete evidence for this view. Buddingh,¹⁵⁹ however, has described a type of diarrhea, epidemic in newborn infants, associated with stomatitis, which he believes to be of viral origin. By inoculating stools or scrapings from the buccal cavity onto the scarified conjunctiva of the rabbit, a transmissible disease was initiated. Further work is needed in this important field.

INFECTION WITH THE SALIVARY GLAND VIRUS

This condition, also known as inclusion disease, is of interest because of the fact that it is a latent infection which at times may seriously damage vital organs. The presence of the virus is indicated by the occurrence of very large granular inclusions which distend the nuclei of infected cells and by smaller cytoplasmic inclusions which are less frequent and conspicuous. The virus derives its name from the fact that its inclusions are most often seen in the ductal epithelium of the salivary glands. Studies of routine postmortem material have shown that about 10 per cent of all infants dying, regardless of the cause of death, have the characteristic inclusions in the salivary glands. Similar inclusions may be found in the salivary glands of a large percentage of apparently normal guinea pigs, mice, and other animals, but evidence to date indicates that each virus is infective only for the species of animal in which it occurs.

In human infants, generalized infection is much more common in association with whooping cough than in cases selected at random but uncomplicated infection with this virus is a relatively common cause of death in infants.¹⁶⁰ Pneumonia apparently caused by this virus has been described. Inclusions may be present in a large percentage of all tubular epithelial cells in the kidney, in which case uremia may occur (see Fig. 219). In another case seen recently, severe jaundice was the outstanding clinical symptom, and there was massive involvement microscopically of the liver cord cells. Intestinal ulceration and encephalitis have also been noted.¹⁶⁰

In adults, the virus causes a very characteristic necrotizing interstitial pneumonitis, which is readily recognized by the presence of the large inclusion-bearing cells. Since its original description by McMillan,¹⁶¹ several other identical cases have been brought to the attention of the author.

Hartz has also described the inclusions in gastrointestinal ulcers and inflammatory lesions excised surgically.¹⁶²

This virus apparently is the cause of some cases of nontoxoplasmic calcifying encephalitis in infants.

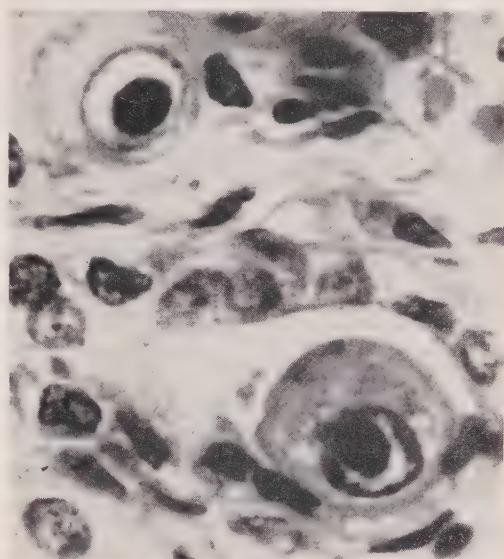


Fig. 219.—Huge nuclear inclusions in renal tubular epithelial cells. From a case of inclusion disease in an infant. Renal involvement was sufficient to cause uremia.

THE COXSACKIE VIRUSES

Dalldorf and Sickles, in 1948, reported the isolation in suckling mice of a new virus from the feces of poliomyelitis patients.¹⁶³ Subsequent work by various investigators has resulted in the frequent isolation of similar viruses from human feces and throat washings, from sewage, and from flies. At present, at least seven antigenically different types have been recognized. Strains have been isolated from individuals with a wide variety of clinical manifestations,¹⁶⁴ simulating such divergent diseases as poliomyelitis, aseptic meningitis, epidemic pleurodynia, acute appendicitis, sinusitis, influenza, infectious mononucleosis, and roseola infantum subitum. For these reasons, it is customary to speak of the "coxsackie group of viruses."

Viruses of this group have one biologic characteristic in common, namely, their ability to cause illness in suckling mice and hamsters, while mature animals of these species are unsusceptible. Kilbourne and Horsfall, however, found that adult mice may be lethally infected if a single injection of cortisone is given before inoculation with the virus.¹⁶⁵ The lesions produced in mice are inflammation and necrosis of skeletal muscles, encephalitis, and inflammatory changes in the fat pads, heart, and other organs. Certain strains cause lesions only in the skeletal muscles.

It is clear that infection with viruses of this group is widely prevalent in the United States, and it is to be expected that our knowledge of the diseases caused by these viruses will in-

crease rapidly. Diagnosis may be made by the inoculation of suckling mice and by demonstrating increasing titers of complement fixation and neutralizing antibodies in the patient's blood.

CAT-SCRATCH DISEASE*

This is a self-limited, inflammatory disease resulting from the scratch of a cat and thought to be caused by an unidentified virus. The symptoms are painful regional lymphadenopathy, general malaise, low-grade fever, and, sometimes, a skin lesion at the site of the inoculation. The most characteristic features of cat-scratch disease are found in the involved lymph nodes, and similar changes may be found in the skin lesion. The histologic appearance depends on the age of the disease. In the early stage the lymph nodes show prominent follicles

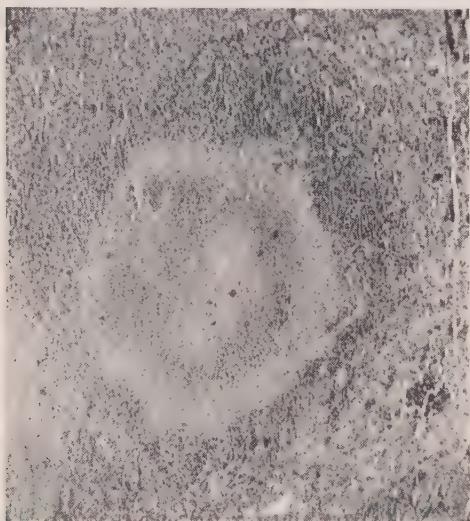


Fig. 220.—Abscess of cat-scratch disease in a lymph node.

and nonspecific lymphadenitis, but the more distinguishing lesions appear later, as multiple granulomas of varying sizes appear. In the advanced stage of the disease abscesses are formed, with necrotic centers surrounded by a zone of histiocytes, outside of which the lymphocytes are compact and there are many polymorphonuclear leukocytes and plasma cells. The inflammatory cells usually fill the peripheral sinuses and involve the pericapsular tissues. Giemsa stains show scattered, large, elongated cells filled with small, purple granules which are suggestive of a virus disease. It is impossible, on histologic grounds alone, to differentiate cat-scratch disease from lymphopatia venereum or tularemia. The diagnosis must be confirmed by collateral clinical data and by the intradermal injection of an antigen developed from pus withdrawn from a suppurative node in a known case.

*Contributed by Dr. T. Winship.

DISEASES NOT DISCUSSED

In all, at least sixty-two diseases of man are known or generally believed to be caused by viruses. The following are not discussed in this chapter because they are considered elsewhere in the book: infectious mononucleosis, infectious polyneuritis, infectious hepatitis, lymphogranuloma venereum, and warts. Excluded because of their rarity or their relative unimportance to the pathologist are Australian X disease, B virus infection, swineherd's disease, louping ill, pretibial fever, Rift Valley fever, Colorado tick fever, encephalomyocarditis, Newcastle disease, equine infectious anemia, ovine pustular dermatitis, and foot-and-mouth disease. For information concerning these diseases the student is referred to the textbook edited by Rivers.⁵

References

General

1. Mudd, S., and Anderson, T. F.: J. A. M. A. **126**: 561, 632, 1944 (electron microscope studies of bacteria, rickettsiae, and viruses).
2. Pinkerton, H.: Bact. Rev. **6**: 37, 1942 (nature and classification of rickettsiae).
3. Stanley, W. M.: Medicine **18**: 431, 1939 (viruses).
4. Rivers, T. M.: Bull. New York Acad. Med. **14**: 383, 1938 (viruses).
5. Viral and Rickettsia: Diseases of Man, edited by Rivers, Philadelphia, 1948, J. B. Lippincott Co.
6. Van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, New York, 1948, Thomas Nelson & Sons.

Typhus Fever

7. da Rocha-Lima, H.: Klin. Wchnschr. **53**: 567, 1916.
8. Pinkerton, H.: in Musser's Internal Medicine, ed. 5, Philadelphia, 1951, Lea & Febiger.
9. Nicolle, C.: Compt. rend. Acad. Sc. **149**: 486, 1911.
10. Strong, R. P., and others: Typhus Fever With Particular Reference to the Serbian Epidemic, Cambridge, 1920, Harvard University Press.
11. Wheeler, C. M.: Am. J. Pub. Health, **36**: 119, 1946.
12. Brill, N. E.: Am. J. M. Sc. **139**: 484, 1910.
13. Maxcy, K. F.: Pub. Health Rep. **41**: 2967, 1926.
14. Dyer, R. E., Rumreich, A., and Badger, L. F.: Pub. Health Rep. **46**: 334, 1931.
15. Zinsser, Hans: Am. J. Hyg. **25**: 430, 1937.
16. Wolbach, S. B., Todd, J. L., and Palfrey, F. W.: The Etiology and Pathology of Typhus, Cambridge, 1922, Harvard University Press.
17. Topping, N. H., and Shear, M. J.: Pub. Health Rep. **59**: 1671, 1944.
18. Allen, A. C., and Spitz, S.: Am. J. Path. **21**: 603, 1945 (comparative study of tsutsugamushi and other rickettsial diseases).
19. Woodward, T. E., and Bland, E. F.: J. A. M. A. **126**: 287, 1944 (clinical features).
20. Yeomans, A., Snyder, J. C., Murray, E. S., Ecke, R. S., and Zarafonetis, C. J. D.: Ann. Int. Med. **23**: 711, 1945 (azotemia in typhus).

Spotted Fever

21. Parker, R. R.: J. A. M. A. **110**: 1185, 1273, 1938.
22. Davis, G. E., and Parker, R. R.: Pub. Health Rep. **49**: 423, 1934.
23. Wolbach, S. B.: J. Med. Research **41**: 1, 1919.
24. Pinkerton, H., and Hass, G. M.: J. Exper. Med. **56**: 151, 1932.
25. Lillie, R. D.: Pub. Health Rep. **46**: 2840, 1931.
26. Huebner, R. J., Stamps, P., and Armstrong, C.: Pub. Health Rep. **61**: 1605, 1946 (ricketsialpox).

Tsutsugamushi Disease

27. Blake, F. G., Maxcy, K. F., Sadusk, J. F., Jr., Kohls, G. M., and Bell, E. J.: Am. J. Hyg. 41: 243, 1945.
 28. Ishiwara, K., and Ogata, N.: Tokyo Ijishinshi, No. 2581, p. 1555, 1928.
 29. Nagayo, M., Miyagawa, Y., Mitamura, T., Tamiya, T., Sato, K., Hazato, H., and Imamura, A.: Japan. J. Exper. Med. 9: 87, 1931.

Q Fever

30. Derrick, E. H.: M. J. Australia 2: 281, 1937.
 31. Dyer, R. E.: Pub. Health Rep. 54: 1229, 1939.
 32. Am. J. Hyg. 44: 1, 1946 (twelve papers by many authors).

Trench Fever

33. Trench Fever: Report of Commission on Trench Fever, American Red Cross Med. Res. Committee, London, 1918, Oxford University Press.
 34. Bacot, A.: Brit. M. J. 1: 156, 1921.

Laboratory Diagnosis of Rickettsial Diseases

35. Pinkerton, H.: Diagnosis and Classification of the Rickettsial Diseases. Virus and Rickettsial Diseases, Harvard School of Public Health Symposium Volume, Harvard University Press, 1940.
 36. Bengtson, I. A., and Topping, N. H.: Am. J. Pub. Health 32: 48, 1942 (complement fixation).
 37. Cox, H. R.: Pub. Health Rep. 53: 2241, 1938 (growth of rickettsiae in yolk sac).

Bartonellosis

38. Weinman, D.: Tr. Am. Philosophical Soc. 33: Part III, 243, 1944 (general review).
 39. Geiman, Q. M.: Proc. Soc. Exper. Biol. & Med. 47: 329, 1941 (culture media).
 40. Stanton, M. F., Laskowski, L., and Pinkerton, H.: Proc. Soc. Exper. Biol. & Med. 74: 705, 1950.
 41. Pinkerton, H., and Weinman, D.: Proc. Soc. Exper. Biol. & Med. 37: 591, 1937 (Carrión's disease).

Properties of Virus

42. Stanley, W. M.: The Harvey Lectures 33: 170, 1937-38 (virus proteins).
 43. Moore, A. E.: Cancer 2: 525, 1949.
 44. Pinkerton, H., and Swank, R. L.: Proc. Soc. Exper. Biol. & Med. 45: 704, 1940.
 45. Cowdry, E. V.: Am. J. Clin. Path. 10: 133, 1940 (inclusions).
 46. Findlay, G. M.: Handbuch der Virusforschung, (Doerr und Hallauer) Erste Halfte. Wien, 1938, Julius Springer, p. 341 (significance of intranuclear inclusions).
 47. Pinkerton, H.: Am. J. Clin. Path. 20: 201, 1950.
 48. Goodpasture, E. W.: Science 77: 119, 1933.
 49. Yanamura, H. Y., and Meyer, K. F.: J. Infect. Dis. 68: 1, 1941.
 50. Tyzzer, E. E., Sellards, A. W., and Bennett, B. L.: Science 88: 505, 1938.

Laboratory Study of Viruses

51. Stimpert, F. D.: J. Pediat. 18: 429, 1941.
 52. Sulkin, S. E., and Harford, C. G.: J. A. M. A. 122: 643, 1943 (laboratory diagnosis).
 53. Beveridge, W. I. B., and Burnet, F. M.: Medical Res. Council. Special Report Series No. 256, London, 1946.
 54. Goodpasture, E. W.: J. Pediat. 18: 440, 1941 (pathology of virus diseases).
 55. Rous, P.: J. Exper. Med. 12: 696, 1910 (fowl sarcoma).

Rabies

56. Webster, L. T.: Rabies, New York, 1942, The Macmillan Co.

57. Schukru-Aksel, I.: Arch. f. Psychiat. 104: 469, 1935.
 58. Goodpasture, E. W.: Am. J. Path. 1: 547, 1925.
 59. Webster, L. T., and Dawson, J. R., Jr.: Proc. Soc. Exper. Biol. & Med. 32: 570, 1935.

Poliomyelitis

60. Paul, J. R., Salinger, R., and Trask, J. D.: J. A. M. A. 98: 2262, 1932 (abortive form).
 61. Paul, J. R., and Trask, J. D.: J. Exper. Med. 56: 319, 1932 (abortive form).
 62. Jungblut, C. W., and Sanders, M.: J. A. M. A. 116: 2136, 1941 (transmission to monkeys).
 63. Armstrong, C.: Pub. Health Rep. 54: 1719, 1939 (transmission to rats).
 64. Armstrong, C.: Pub. Health Rep. 54: 2302, 1939 (experimental transmission).
 65. Peers, J. H.: Arch. Path. 32: 928, 1941 (comparison of lesions in man and in monkeys).
 66. Luhan, J. A., and Hurst, E. W.: Arch. Neurol. & Psychiat. 37: 479, 1937 (histopathology of experimental poliomyelitis).
 67. Enders, J. F., Weller, T. H., and Robbins, F. C.: Science 109: 85, 1949.
 68. Aycock, W. L., and Kramer, S. D.: J. Prev. Med. 4: 189, 1930 (immunity).
 69. Jungblut, C. W., and Dallendorf, G.: Am. J. Pub. Health 33: 169, 1943.
 70. Trask, J. D., Vignec, A. J., and Paul, J. R.: J. A. M. A. 111: 6, 1938 (virus in stools).
 71. Sabin, A. R., and Ward, R.: Science 94: 590, 1941 (flies as carriers).
 72. Francis, T., Jr., Krill, C. E., Toomey, J. A., and Mack, W. N.: J. A. M. A. 119: 1392, 1942 (poliomyelitis following tonsillectomy).
 73. Editorial: J. A. M. A. 116: 2506, 1941 (effect of trauma and strain).
 74. Hurst, E. W.: J. Path. & Bact. 34: 331, 1931 (inclusions).
 75. Foster, C., Jones, J. H., Henle, W., and Dorfman, F.: Proc. Soc. Exper. Biol. & Med. 51: 215, 1942.

Encephalitis Lethargica

76. Von Economo, C. V.: Wien. Klin. Wchnschr. 30: 581, 1917.
 77. Flexner, S., and Amoss, H. L.: J. Exper. Med. 41: 215, 233, 357, 1925.
 78. Dawson, J. R., Jr.: Am. J. Path. 9: 7, 1933.
 79. Zinsser, H.: Arch. Path. 6: 271, 1928.
 80. Broun, G. O.: Encephalitis and Other Virus Infections of the Central Nervous System. Oxford Medicine, vol. VI, chap. III, New York, 1950, Oxford University Press.
 81. Macnalty, A. S.: Brit. J. Exper. Path. 2: 141, 1921.

St. Louis Encephalitis

82. Webster, L. T., and Fite, G. L.: Science 78: 463, 1933.
 83. Hemplemann, T. C.: J. A. M. A. 103: 733, 1934 (symptoms and diagnosis).
 84. Smith, M. G., Blattner, R. J., and Heys, F. M.: Science 100: 362, 1944 (isolation of virus from chicken mites).
 85. Hammon, W. McD., and Reeves, W. C.: Proc. Soc. Exper. Biol. & Med. 51: 142, 1942 (mosquito vector).
 86. McCordock, H. A., Collier, W., and Gray, S. H.: J. A. M. A. 103: 822, 1934 (pathologic changes).

Japanese B Encephalitis

87. Smith, M. G.: South. M. J. 33: 522, 1940.
 88. Webster, L. T.: J. A. M. A. 116: 2840, 1941.

Equine Encephalomyelitis

89. Tyzzer, E. E., Sellards, A. W., and Bennett, B. L.: Science 88: 505, 1938.
 90. Fothergill, L. R. D., and associates: New England J. Med. 219: 411, 1938.
 91. Hurst, E. W.: J. Exper. Med. 59: 529, 1934.

Lymphocytic Choriomeningitis

92. Armstrong, C., Wallace, J. J., and Ross, L.: Pub. Health Rep. 55: 1222, 1940 (mouse reservoir).

Viral Pneumonias of Infants

93. Smadel, J. E., Green, R. H., Paltauf, R. M., and Gonzales, T. A.: Proc. Soc. Exper. Biol. & Med. **49**: 683, 1942 (human fatalities).
 94. Armstrong, C., and Lillie, R. D.: Publ. Health Rep. **49**: 1019, 1934 (experimental).
 95. Findlay, G. M., and Stern, R. O.: J. Path. & Bact. **43**: 327, 1936 (pathologic changes).
 96. Zarafonetis, C. J. D.: New England J. Med. **230**: 567, 1944 (meningoencephalitis in lymphogranuloma venereum).
 97. Casals, J., and Webster, L. T.: Science **97**: 246, 1943 (relation between Russian spring-summer encephalitis and louping-ill viruses).

Herpes Encephalitis

98. Smith, M. G., Lenette, E. H., and Reames, H. R.: Am. J. Path. **17**: 55, 1941.
 99. Majamud, N., Haymaker, W., and Pinkerton, H.: Am. J. Path. **26**: 133, 1950.

Postinfection Encephalitis

100. Putnam, T. J.: Bull. New York Acad. Med. **17**: 337, 1941.
 101. Hurst, E. W., and Fairbrother, R. W.: J. Path. & Bact. **33**: 463, 1930 (experimental vaccinal encephalitis).
 102. Bassoe, P., and Grinker, R. R.: Arch. Neurol. & Psychiat. **23**: 1138, 1930 (rabies vaccine encephalomyelitis).
 103. Rivers, T. M., and Schwentker, F. F.: J. Exper. Med. **61**: 689, 1935.

Influenza

104. Mote, J. R.: General Considerations of Virus Diseases of the Respiratory Tract, and Human and Swine Influenza, Virus and Rickettsial Diseases, Harvard School of Public Health Symposium Volume, Cambridge, 1940, Harvard University Press, pp. 409-516.
 105. Smith, W., Andrewes, C. H., and Laidlaw, P. P.: Lancet **2**: 66, 1933 (influenza virus).
 106. Andrewes, C. H., Laidlaw, P. P., and Smith, W.: Lancet **2**: 859, 1934 (influenza virus).
 107. Wolbach, S. B., and Frothingham, C.: Arch. Int. Med. **32**: 571, 1923 (pathologic changes).
 108. MacCallum, W. G.: Johns Hopkins Hosp. Rep. **20**: 149, 1921 (pathologic changes).
 109. Hirst, G. K.: J. Exper. Med. **75**: 49, 1942 (quantitative determination of influenza virus and antibodies by means of red cell agglutination).
 110. Michael, M. J.: J. A. M. A. **118**: 869, 1942 (staphylococcus pneumonia complicating influenza).

Common Cold

111. Dochez, A. R., and associates: J. Exper. Med. **43**: 415, 1926; **47**: 493, 1928; **52**: 701, 1930; **53**: 447, 1931; and **63**: 559, 1936; also J. A. M. A. **110**: 177, 1938 (various studies on the common cold).

Psittacosis and Ornithosis

112. Enders, T. F.: Psittacosis, Virus and Rickettsial Diseases, Harvard School of Public Health Symposium Volume, Cambridge, 1940, Harvard University Press, p. 528.
 113. Meyer, K. F.: Medicine **21**: 175, 1942.
 114. Eaton, M. D., Martin, W. P., and Beck, M. D.: J. Exper. Med. **75**: 21, 1942 (antigenic relationship of viruses of meningopneumonitis and lymphogranuloma venereum).
 115. Lillie, R. D.: I. The Pathology of Psittacosis in Man. II. The Pathology of Psittacosis in Animals and the Distribution of Rickettsia Psittaci in the Tissues of Man and Animals. National Institute of Health Bulletin, No. 161, Washington, D. C., 1933, U. S. Public Health Service.
 116. Bedson, S. P.: Brit. J. Exper. Path. **13**: 65, 1932 (elementary bodies).
 117. Pinkerton, H., and Moragues, V.: J. Exper. Med. **75**: 575, 1942.

Primary Atypical Pneumonia

121. Kneeland, Y. Jr., and Smetana, H. F.: Bull. Johns Hopkins Hosp. **67**: 229, 1940.
 122. Longcope, W. T.: Bull. Johns Hopkins Hosp. **67**: 268, 1940.
 123. Meiklejohn, G.: Proc. Soc. Exper. Biol. & Med. **54**: 181, 1943.

Smallpox and Vaccinia

124. Russell, F. F.: Smallpox and Vaccination, Oxford Medicine, vol. V, chap. 23, New York, 1942, Oxford University Press.
 125. Russell, F. F.: The Epidemiology and Control of Variola Virus and Rickettsial Diseases, Cambridge, 1940, Harvard University Press, p. 176.
 126. Goodpasture, E. W., Woodruff, A. M., and Buddingh, G. J.: Am. J. Path. **8**: 271, 1932 (vaccinia).
 127. Lillie, R. D.: Arch. Path. **10**: 241, 1930 (pathologic changes).
 128. Ross, R. A.: Generalized Vaccinia, Virus and Rickettsial Diseases, Cambridge, 1940, Harvard University Press, p. 217.

Chicken Pox

129. Johnson, H. N.: Arch. Path. **30**: 292, 1940.
 130. Frank, L.: Arch. Path. **50**: 457, 1950.
 131. Bullova, J. G. M., and Wishik, S. M.: Am. J. Dis. Child. **49**: 923, 1935 (complications).
 132. Stokes, J. Jr.: in Viral and Rickettsial Diseases of Man.⁵

Measles

133. Denton, J.: Am. J. M. Sc. **169**: 531, 1925 (pathologic changes).
 134. Warthin, A. S.: Arch. Path. **11**: 864, 1931 (giant cells in prodromal stages).
 135. Gordon, H., and Knighton, H. T.: Am. J. Path. **17**: 165, 1941 (experimental).

German Measles

136. Habel, K.: Publ. Health Rep. **57**: 1126, 1942 (transmission to monkeys).
 137. Greenthal, R. M.: Arch. Pediat. **62**: 53, 1945 (as a cause of congenital malformations).

Molluscum Contagiosum

138. Goodpasture, E. W., and Woodruff, C. E.: Am. J. Path. **7**: 1, 1931.

Herpes Simplex

139. Warren, S. L., Carpenter, C. M., and Boak, R. A.: J. Exper. Med. **71**: 155, 1940.
 140. Goodpasture, E. W., and Teague, O.: J. M. Res. **44**: 121, 1923.
 141. Hass, G. M.: Am. J. Path. **11**: 127, 1935.
 142. Smith, M. G.: Personal communications.
 142a. Zuelzer, W. W.: Am. J. Dis. Child. **83**: 421, 1952.

Herpes Zoster

143. Goodpasture, E. W., and Anderson, K. A.: Am. J. Path. **20**: 447, 1944.
 144. Stokes, J.: In Rivers: Viral and Rickettsial Diseases of Man.⁵

Mumps

145. Wasselhoeft, C.: Mumps: Its Glandular and Neurologic Manifestations, Virus and Rickettsial Diseases, Cambridge, 1940, Harvard University Press, p. 309.

146. Johnson, C. D., and Goodpasture, E. W.: Am. J. Path. 12: 495, 1936 (histopathology in monkeys).
 147. Enders, J. F.: J. Pediat. 29: 129, 1946.

Yellow Fever

148. Soper, F. L.: Yellow Fever, in Bercowitz: Clinical Tropical Medicine, New York, 1944, Paul B. Hoeber, Inc.
 149. Hudson, N. P.: Am. J. Path. 4: 395, 1928 (pathologic changes).
 150. Lloyd, W.: Am. Heart J. 6: 504, 1931 (myocardial lesions).
 151. Theiler, M., and Smith, H. H.: J. Exper. Med. 65: 787, 1937 (immunization).
 152. Soper, F. L.: Am. J. Trop. Med. 17: 457, 1937.
 153. Klotz, O., and Belt, T. H.: Am. J. Path. 6: 663, 1930 (pathologic changes).

Trachoma

154. Julianelle, L. A.: Trachoma, in Bercowitz: Clinical Tropical Medicine, New York, 1944, Paul B. Hoeber, Inc.
 155. Thygeson, P.: Trachoma and Inclusion Conjunctivitis, in Rivers: Viral and Rickettsial Diseases of Man.⁵

Epidemic Keratoconjunctivitis

156. Sanders, M., Gulliver, F. D., Forchheimer, L. L., and Alexander, R. C.: J. A. M. A. 121: 250, 1943.
 157. Cheever, F. S.: Proc. Soc. Exper. Biol. & Med. 77: 125, 1951.

Dengue and Phlebotomus Fever

158. Sabin, A. B.: In Rivers: Viral and Rickettsial Diseases of Man.⁵

Viral Enteritis

159. Buddingh, G. J.: South. Med. J. 39: 382, 1946.

Salivary Gland Virus

160. Wyatt, J. P., Saxton, J., Lee, R. S., and Pinkerton, H.: J. Pediat. 36: 271, 1950.
 161. McMillan, G. C.: Am. J. Path. 23: 995, 1947.
 162. Hartz, P. H., and van de Stadt, F. R.: Am. J. Clin. Path. 18: 148, 1943.

The Coxsackie Viruses

163. Dalldorf, G., and Sickles, G. M.: Science 108: 61, 1948.
 164. Dalldorf, G., Curnen, E. C., and Melnick, J. L.: Bull. New York Acad. Med. 26: 329, 1950.
 165. Kilbourne, E. D.: and Horsfall, F. S., Jr.: Proc. Soc. Exper. Biol. & Med. 77: 135, 1951.

Cat-Scratch Disease

166. Greer, W. E. R., and Keefer, C. F.: New England J. Med. 244: 545, 1951.
 167. Daniels, W. B., and MacMurray, F. G.: Arch. Int. Med. 88: 736, 1951.
 168. Hedinger, C., Usteri, C., Wegmann, T., and Wortmann, F.: Dermatologica 104: 101, 1952.

Chapter 15

FUNGUS INFECTIONS

ROGER D. BAKER

Fungus or mycotic diseases are caused by the vegetable parasites known as fungi. These infections are usually chronic. They vary in seriousness. Some are only nuisances, while others cause death. The superficial fungus infections, like "athlete's foot," are common, and important on that account. The deep infections, like blastomycosis, are rare, but are sufficiently frequent that they must be considered in the differential diagnosis of obscure infections.

FUNGI

Fungi are plants containing no chlorophyl and devoid of leaves, stems, and roots. Those belonging to the genus *Actinomyces* (and *Nocardia*) are higher bacteria, as thick as tubercle bacilli but with the feature of branching. Nearly all the other fungi (Eumycetes or true fungi) are thicker than *Actinomyces*, and more complicated in form. The true fungi grow either as filaments (hyphae) or as rounded bodies (spores). Most of the true fungi belong to the group of Fungi Imperfecti in which the sexual cycle is unknown. Among those in which the sexual cycle is known are the Phycomycetes, having non-septate hyphae. *Mucor* is an example of this group. Most others have septate or segmented hyphae. The Basidiomycetes or mushrooms comprise another group with a known sexual cycle. Mushrooms, however, are not infectious, but the poisonous ones are toxic when ingested.

Reproduction of fungi in human tissues is brought about by budding, septation, or endosporulation. A bud is a rounded embryonic shoot which enlarges and finally becomes free from the parent cell. The process of septation is characterized by the formation of septa within a parent cell. Endosporulation designates the formation of spores within a parent cell.

CLASSIFICATION OF FUNGI IN TISSUES

A grouping of fungi according to the morphology of the fungus in human tissues is used in the presentation of the disease entities of this chapter.

- Group 1. Filaments (hyphae) only.
- Group 2. Rounded bodies only.
- Group 3. Both filaments and rounded bodies.

An amplification of this classification follows, and the method of reproduction in tissues is indicated. In addition, there is a subgrouping based on the form of the fungus in culture. Some fungi send out hyphae when cultured on glucose agar at room temperature, exhibiting pleomorphism.

I. FILAMENTS (HYPHAE) ONLY

A. Hyphae in cultures.

- 1. *Actinomyces bovis*. Anaerobic.
Thin, branching hyphae.
Grains usual in tissues.
- 2. *Nocardia asteroides*. Aerobic.
Thin, branching hyphae.
Grains less usual in tissues.

II. ROUNDED BODIES ONLY

A. Simple cells in culture.

- 1. *Cryptococcus neoformans*. Budding.
- B. Hyphae and spores (reproductive round or oval bodies) on glucose agar at room temperature.
 - 1. *Blastomyces dermatitidis*. Budding.
 - 2. *Blastomyces brasiliensis*. Budding.
 - 3. *Histoplasma capsulatum*. Budding.
 - 4. *Sporotrichum schenckii*. Budding.
 - 5. *Hormodendrum sp.* and *Phialophora verrucosa*. Chromoblastomycosis.
Septation (formation of septae).
 - 6. *Coccidioides immitis*. Endosporulation.
- C. Not cultured.
 - 1. *Rhinosporidium seeberi*. Endosporulation.

III. FILAMENTS AND ROUNDED BODIES

A. Hyphae and spores in cultures.

- 1. *Candida albicans*. Pseudohyphae.
- 2. *Aspergillus sp.*
- 3. *Mucor*. Thick, nonseptate hyphae.
- 4. *Madurella sp.*, *Monosporium apiospermum*, etc. Maduromycosis. Grains.
- 5. *Trichophyton*, *Microsporum*, *Epidermophyton*. Dermatophytes.

B. Not cultured.

- 1. *Malassezia furfur*.
Tinea versicolor.

INJURY PRODUCED BY FUNGI

No one tissue change is entirely characteristic of, or pathognomonic of, fungus disease. All of the usual inflammatory and repair processes, and also necrosis, may occur.

Fungi may grow on the skin and hair without producing inflammatory reaction and are essentially saprophytic. Even the pathogenic organisms causing tinea pedis ("athlete's foot") may live in the horny layer of the skin and in the nails, like saprophytes, and cause no inflammatory reaction (Fig. 254). On occasion, because of moisture or some other factor, they assume a pathogenic role and produce inflammation.

to the release of endotoxins when the organisms become necrotic.

Pus production is exemplified in several of the mycoses (Figs. 222, 224, 229, 230, 231, 233, 243, and 249). The neutrophile is usually the primary reacting cell. In some instances, however, the macrophage or the giant cell may be the primary reacting cell. Caseous necrosis and tubercles may occur. However, the tubercles of fungus infections tend to be

Fig. 222.

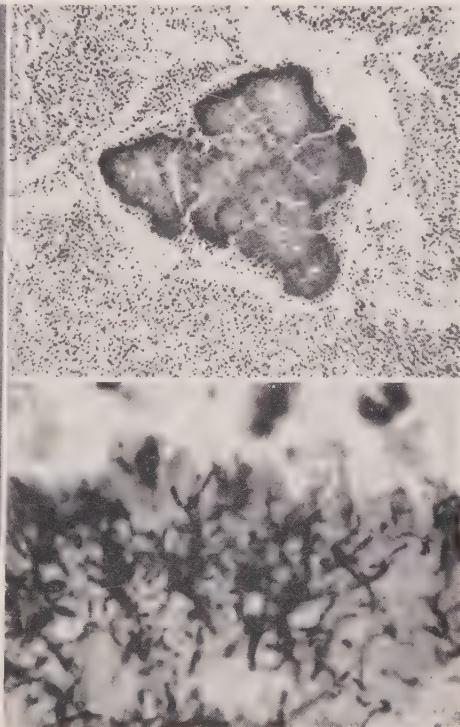


Fig. 221.

Fig. 221.—Actinomycosis of face, showing swelling and orifices of sinuses. (Photograph by courtesy of Dr. A. Gonzales Ochoa.)

Fig. 222.—Granule or grain of *Actinomyces bovis*, surrounded by pus cells.

Fig. 223.—Edge of colony in Fig. 222, stained by the method of Gram to show the branching hyphae.

The pathogenic fungi which invade beneath the body surface usually produce chronic suppuration with fibrosis. Most fungi are relatively inert, do not produce exotoxins, and act as foreign bodies. Not infrequently the organisms are found within giant cells (Figs. 234 and 244). It is difficult to say how much of the inflammatory response is due to the fungi acting as foreign bodies and how much

more like abscesses. As the chronic inflammation continues, the repair process is initiated and, in time, scar tissue is a prominent component of the reaction. The resulting mass resembles a neoplasm and is called a granuloma (Fig. 248).

Some deviations from these generalities are to be noted. For example, the essential lesion of histoplasmosis consists of phagocytosis of the organisms by the cells of the reticuloendo-

thelial system (Fig. 236). This is more like the process of storage than of inflammation.

Extensive fungus infections may be present without systemic symptoms. Thus, patients with the large localized lesions of chromoblastomycosis or mycetoma or even with early systemic infections may be ambulatory and free from fever. As generalized infections persist, however, there is usually fever, leukocytosis, and toxemia. In histoplasmosis, leukopenia is more frequent than leukocytosis, because of the fungus parasites in the reticulo-endothelial cells of the bone marrow.

Mycetoma is one of the few designations in fungus terminology in which the disease is not named from the specific causative fungus. It may be caused by a variety of species and genera of fungi.

Hypersensitivity of the body to fungi can frequently be demonstrated. For example, if a suspension of a killed culture of *Coccidioides immitis* is injected into the skin of a person who has had coccidioidomycosis, a focal inflammatory response occurs which is analogous to the tuberculin reaction. Hypersensitivity to common saprophytic fungi can be demonstrated in some

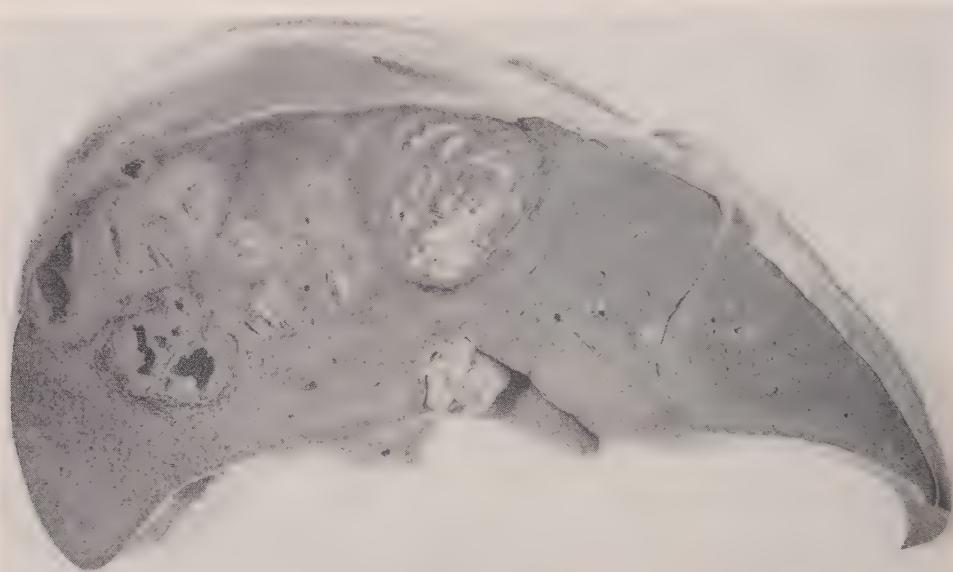


Fig. 224.—Actinomycosis of the liver due to *A. bovis*. The disease began in the cecum or appendix, forming a retrocecal abscess which ruptured to the skin surface in the right inguinal region.

Fungi usually enter the body through the skin, the respiratory tract, or the digestive tract. When the organism enters the skin, it is probably through a small wound. Sporotrichosis is a good example because it follows a puncture by a thorn or other sharp object with inoculation of the organism into the skin. Puncture wounds appear to be important also in the initiation of mycetomas. Aspiration of fungus organisms into the respiratory tract apparently accounts for the deep infections of coccidioidomycosis, cryptococcosis, and blastomycosis. The digestive tract is the usual portal of entry in actinomycosis, the organisms being derived from the periodontal tissues or tonsils where they occur as saprophytes.

Mycetoma connotes a tumorlike swelling caused by a fungus organism. In practice, the term is limited to such a swelling occurring on an extremity, nearly always on foot or leg. Furthermore, in practice the term is limited to a tumorlike swelling in which there are abscesses of the deep tissues and usually of the bones, with sinuses extending to the surface (Fig. 248).

persons who have asthma or hay fever, and these saprophytes may thus be important in the causation of these allergic diseases.

Immune bodies can be demonstrated in the sera of persons with certain fungus infections. For example, in blastomycosis complement-fixing antibodies can often be demonstrated.

The mycoses are protean in their manifestations and often resemble other types of infection and even tumors. For example, generalized blastomycosis is much like a chronic staphylococcal infection. Both may exhibit pyemia and osteomyelitis. There is some resemblance of several of the mycoses to tuberculosis, sometimes based on symptomatology and sometimes on the similarity of tissue response. Cutaneous blastomycosis may simulate carcinoma of the skin. Mycetoma may simulate a tumor of the foot.

The geographic distribution varies according to the type of mycosis. Whereas actinomycosis is world-wide in distribution, South American blastomycosis is restricted to South America. It is not precise to designate the fungus in-

fections as tropical diseases because most of the mycoses are as prevalent in the temperate zones as in the tropics. The tineas, however, are more extensive and severe in the tropics than in more temperate regions.

CLASSIFICATION OF FUNGUS DISEASES

Another classification, based largely upon the anatomical location of the lesions, is as follows:

SUPERFICIAL FUNGUS INFECTIONS

A. Saprophytic

Hair shafts.—*Piedra*. Trichomycosis axillaris. Stratum corneum.—*Tinea versicolor*. Erythrasma.

B. Pathogenic

Skin.—Dermatomycoses: *Tinea pedis*, *eruris*, *imbricata*, *barbae*, *capitis*, *favosa*. Moniliasis. Mucormycosis.

Hair.—Dermatomycoses: *Tinea barbae*, *capitis*, *favosa*.

Nails.—Dermatomycoses: *Tinea unguium*. Moniliasis.

Mucous membranes.—Moniliasis. Rhinosporidiosis. Aspergillosis. Geotrichosis.

DEEP FUNGUS INFECTIONS

A. Localized

Skin and subcutaneous tissues.—Cutaneous blastomycosis, coccidioidomycosis, cryptococcosis, actinomycosis. Chromoblastomycosis. Sporotrichosis.

Skin and mucous membranes.—Histoplasmosis. South American blastomycosis.

Lymph nodes.—Actinomycosis, blastomycosis, histoplasmosis, coccidioidomycosis.

All tissues of extremity, including bone.—Mycetoma. Maduromycosis.

Lungs.—Actinomycosis. Cryptococcosis. Blastomycosis. Primary coccidioidomycosis. Moniliasis. Aspergillosis. Geotrichosis. Penicilliosis.

Abdomen.—Actinomycosis.

Cranial cavity, orbit, sinuses.—Moniliasis. Mucormycosis. Aspergillosis.

B. Generalized (by blood stream)

Pyemias.—Generalized blastomycosis. Secondary coccidioidomycosis. Actinomycosis (porta system especially). Nocardiosis. South American blastomycosis. Sporotrichosis.

Septicemias.—Moniliasis (endocarditis). Histoplasmosis (endocarditis).

Reticulo-endothelial system involvement.—Histoplasmosis (occasionally local).

Affinity for central nervous system.—Cryptococcosis.

Actinomycosis and Nocardiosis.—Actinomycosis denotes the disease caused by the anaerobic *Actinomyces bovis*, and nocardiosis the disease caused by the aerobic *Nocardia (Actinomyces) asteroides*. The term streptothricosis was formerly used instead of nocardiosis.

Actinomycosis as caused by the anaerobic organism is of world-wide occurrence and is the commonest of the deep fungus infections. The organisms inhabit the buccal cavity of man and it is thought that infection of the mucous membranes of the mouth or intestinal tract, or of the lungs, is endogenous in origin, occurring through wounds of the various surfaces.

The commonest form of actinomycosis is the cervicofacial, originating from an infection within the mouth, as, for example, in a tooth socket. The soft tissues at the angle of the jaw become swollen and indurated and the abscesses within the swelling rupture to the surface of the skin or mucous membrane, forming sinuses (Fig. 221). The disease may be chronic, lasting for months and years, but usually is not fatal. The infection may extend along the spine, producing chronic periostitis and osteomyelitis, and it may even extend into the cranial cavity.

The abdominal form of the disease begins in the mucous membrane of the appendix or large bowel and extends to the periappendiceal or pericolic tissues or, by way of the portal venous system, to the liver. Small ulcers may be found in the intestinal mucosa, and abscesses in the retroperitoneal tissues, the psoas muscle, or the abdominal cavity. Extension of these abscesses to the skin results in chronic sinuses in the groin or flank. The abscesses of the liver are characteristically multilocular and surrounded by yellow deposits of fat and by gray scar tissue (Fig. 224). The walls of the abscesses often have a honeycombed appearance due to the presence of numerous smaller abscesses.

Pulmonary actinomycosis may develop as a result of the burrowing of hepatic abscesses through the diaphragm. In the absence of the abdominal form, pulmonary actinomycosis may develop by aspiration. The lesions of the lungs are suppurative, with abscesses; or bronchiec-

THE FUNGUS DISEASE ENTITIES

The diseases due to the bacteria-like fungi, *Actinomyces* and *Nocardia*, are presented first. Then follow those diseases caused by true fungi with rounded or oval cell bodies in tissue; and finally those diseases in which hyphae and spores occur in tissue.

tasis may develop with much fibrosis. The pleura is often infected and later thickened. Lesions may develop in the central nervous system, kidneys, ovaries, or leg (mycetoma). The abdominal, thoracic, and generalized forms of the disease frequently terminate fatally.

Nocardiosis occurs as a mycetoma, a pneumonitis, or as a pyemia.

In actinomycosis the organisms in the lesions occur as colonies which are termed granules or grains (Fig. 222). These can be seen with the naked eye in the pus, as gray or yellow "sulfur" granules.

Fig. 225.



Fig. 226.

Fig. 225.—Minute intracerebral cysts in corpus striatum and white matter due to *Cryptococcus neoformans*.

Fig. 226.—*C. neoformans* within intracerebral cyst.

Fig. 227.—*C. neoformans*. Two organisms showing dark central portions and surrounding grayish-white gelatinous capsules. Figs. 225, 226, and 227 are from the same case.

(Fig. 222). Occasionally, giant cells are found applied to the surface of a granule. At the edge of the abscess, macrophages, often filled with fat, are numerous; while other cells of chronic inflammation, and also scarring occur farther out. Nocardiosis may or may not show granules, and the granules may be yellow or red.

Cryptococcosis.—Cryptococcosis is an infection with *Cryptococcus neoformans*, an organism which occurs as a single budding cell even under greatly varying environmental conditions. The organism has also been designated *Torula histolytica*, and the infection, torulosis. The disease is world-wide.

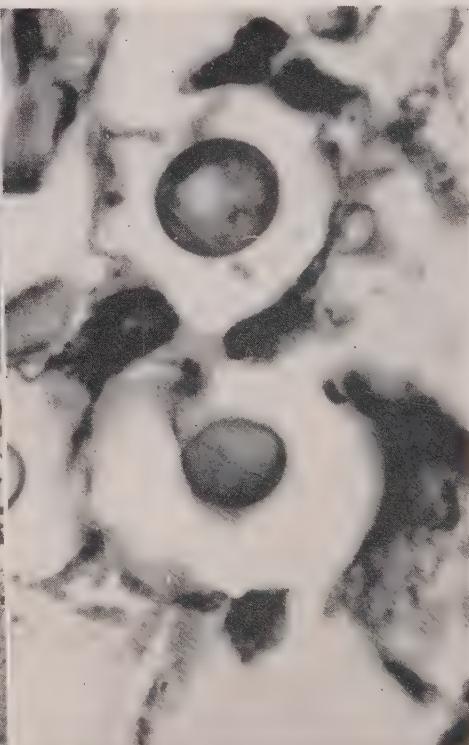
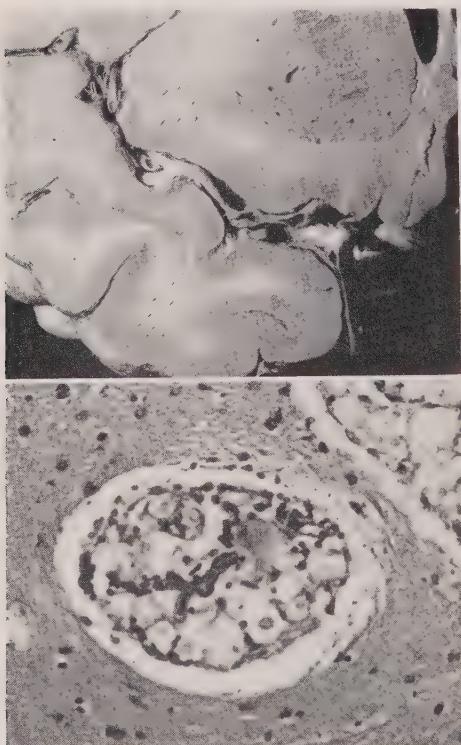


Fig. 227.

The granules are composed of delicate, branching, intertwined, gram-positive filaments (Fig. 223). Bacteria may be present. At the periphery of the granule the filaments may terminate in eosin-staining enlargements or clubs. The granule lies surrounded by pus in a minute abscess

The fungus may produce gelatinous or fibrotic lesions in the lungs. More frequently, however, the chief manifestation of the disease is in the central nervous system with extension from the lungs. Cutaneous lesions are far less common than in blastomycosis, and pus is not produced.

In the spinal fluid, meninges, and perivascular cerebral spaces the organism is found in

large numbers, occurring at times without appreciable inflammatory reaction and at times with a chronic inflammatory response with giant cells and scar tissue. The organisms are often within the giant cells, but in some cases occur in jellylike masses, free as though in pure culture. In tissue the organism characteristically has an extraordinarily thick gelatinous capsule and shows budding. The organisms may form little cysts in the brain (Figs. 225, 226, and 227). The disease usually progresses to a fatal termination over a period of months or years. Some primary pulmonary lesions may heal spontaneously.

tion into the skin or to pulmonary blastomycosis by inhalation. Pulmonary blastomycosis apparently leads to generalized blastomycosis in most cases.

Cutaneous blastomycosis occurs as single or multiple, elevated, red ulcers (Fig. 228). Minute abscesses are visible in the more elevated border. Within the abscesses there are single fungus cells characterized by prominent capsules and by budding (Figs. 229 and 230). The or-

Fig. 229.

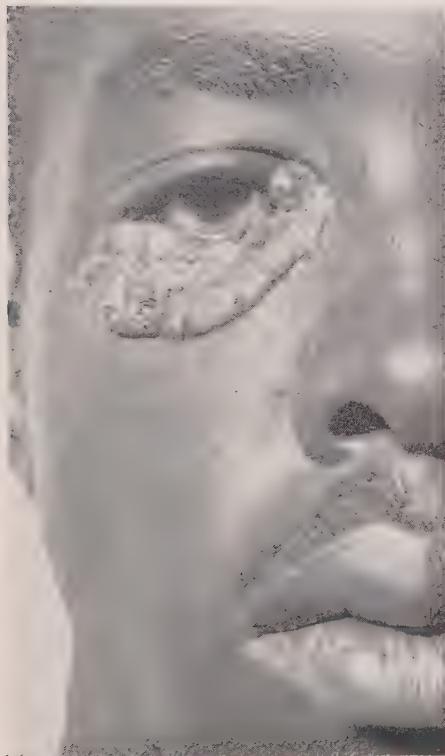


Fig. 228.

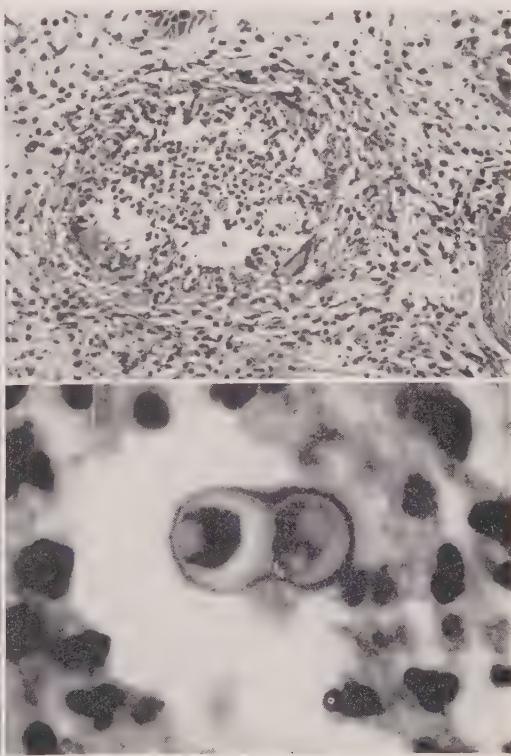


Fig. 230.

Fig. 228.—Cutaneous blastomycosis.

Fig. 229.—Minute abscess with central blastomycete. Giant cells at edge of abscess. Cutaneous blastomycosis.

Fig. 230.—Budding blastomycete from a minute abscess in cutaneous blastomycosis.

Blastomycosis.—Infection with *Blastomyces dermatitidis* is usually called simply blastomycosis, though North American blastomycosis is a more precise designation. The disease has been reported only from the United States, except for a few cases from Canada and England. The infection presumably is derived from some exogenous source and gives rise to primary cutaneous blastomycosis by inocula-

tion into the skin or to pulmonary blastomycosis by inhalation. Pulmonary blastomycosis apparently leads to generalized blastomycosis in most cases. The organism may also be found within giant cells. It is characteristic to have great hypertrophy of the epidermis as a result of the chronic inflammation. Cutaneous blastomycosis usually does not become generalized and it is often completely cured by appropriate therapy.

Generalized blastomycosis is more frequently a pyemia with abscesses in the bones, subcutaneous tissues, and elsewhere.

It usually, though by no means always, ends fatally (Figs. 231, 232, and 233). Organisms are, as a rule, far more numerous in the lesions than in cutaneous blastomycosis (Fig. 235). Caseous nodules may be present and giant cells may be numerous (Fig. 234).

The organisms grow as single budding cells in the tissues, and they maintain this form of growth on blood agar medium at 37° C., but when the organism is grown on glucose agar (Sabouraud's medium) at room temperature, filaments (hyphae) are produced. This same sort of metamorphosis is characteristic of the five subsequently described fungus infections.

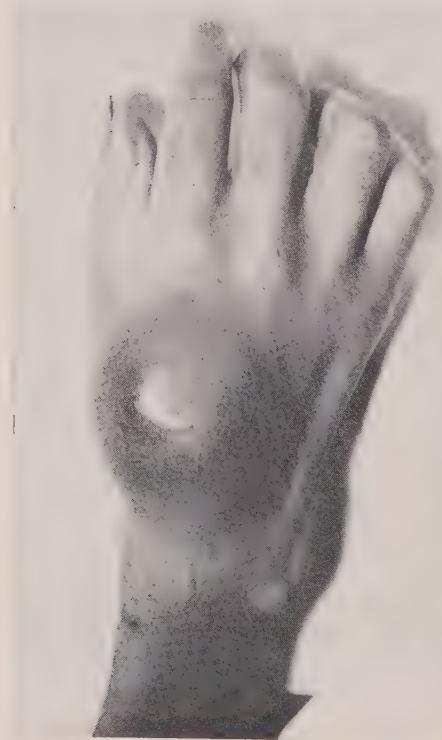


Fig. 231.

Fig. 231.—Subcutaneous abscess in a case of generalized blastomycosis.

Fig. 232.—Patchy pneumonia due to *B. dermatitidis* in generalized blastomycosis.

Complement-fixing antibodies are usually readily demonstrable in the sera of the patients with the generalized form of the disease. No fixation occurs in undiluted sera of patients with the localized form of the disease.

Most patients with blastomycosis, whether of the generalized or systemic

forms, are hypersensitive to the fungus or fungus products, as shown by skin tests with vaccines or extracts of *B. dermatitidis*.

South American blastomycosis is similar to North American blastomycosis, but the causative organism in the tissues is characterized by the presence of multiple buds, and lesions of lymph nodes and mucous membranes are prominent. Paracoccidioidal granuloma is another term for the disease.

Histoplasmosis.—Histoplasmosis is caused by *Histoplasma capsulatum*, a budding fungus organism which is oval and small (1 to 5 microns) in tissues



Fig. 232.

(Fig. 236). It grows in a filamentous form with thick-walled spores in cultures at room temperature.

In its mildest form histoplasmosis is a symptomless and transient pulmonary infection which shows itself later only by the presence of a positive histoplasmin skin test, and sometimes also by a residual

calcified focus in the lungs. Infections of this kind are commonest in the Lower Mississippi Basin, though the disease is world-wide. Occasionally nonfatal pulmonary and extrapulmonary and even systemic histoplasmosis occur.

Of the fatal systemic cases, four-fifths of all the reported cases have occurred in the United States. Persons of all ages are affected, but it has occurred in as many cases during the first year of life

splenomegaly is usual. Necrosis of tissue to form caseous masses may occur, and granulation tissue may form rarely. Ulceration of oral cavity or of intestines is prominent in some cases. Moreover, cases of endocarditis have been reported. Leukopenia and anemia, which are commonly noted, may be correlated with the involvement of the bone marrow.

As the disease progresses, fever and emaciation develop, and in the great

Fig. 234.

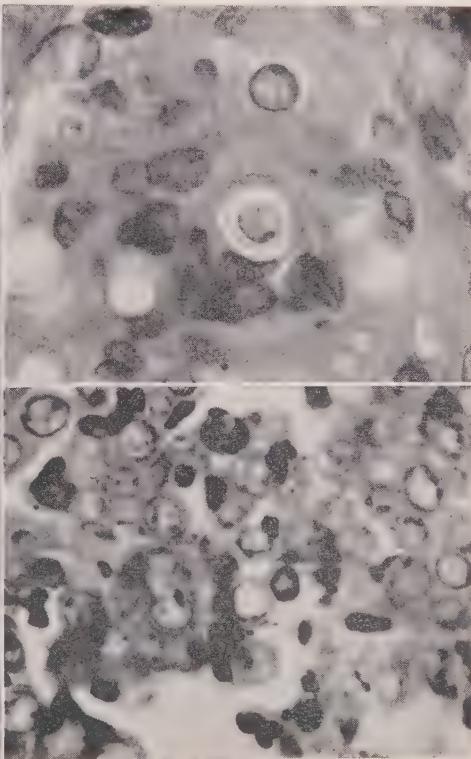


Fig. 234.

Fig. 233.—Osteomyelitis due to *B. dermatitidis* in generalized blastomycosis. To the left is a rib, the lower half of which is destroyed by abscess; to the right is a segment of spine with foci of osteomyelitis in two bodies.

Fig. 234.—Blastomycete with thick capsule in giant cell. Generalized blastomycosis.

Fig. 235.—Blastomycetes in large numbers in a cerebellar lesion. Generalized blastomycosis.

as in any later decade. The mouth is apparently the common portal of entrance. While the infection may be localized, for example in the lungs or skin, it is the unique feature of this fungus to invade the entire reticulo-endothelial system. Therefore, the parasites are most numerous in the liver, spleen, lymph nodes, and bone marrow, and

majority of cases the infection lasts less than one year.

Histoplasmosis resembles the protozoal disease, visceral leishmaniasis, since in both the reticulo-endothelial system is infected and the organisms are similar in appearance.

Sporotrichosis.—In the usual case of sporotrichosis there is a history of injury to the

hand by a sharp object, such as the thorn of a barberry bush. This carries *Sporotrichum schenckii* into the tissues. It is not surprising that the disease occurs in florists and gardeners. A nodule develops and other nodules form along the lymphatic trunks of the arm (Fig. 237). These nodules tend to soften and ulcerate. Microscopically the nodular lesion has a core of necrotic tissue or abscess about which chronic inflammatory reaction and giant cells are seen (Fig. 239). The organism is readily grown in culture from material taken from lesions, but it is present in the human tissues in such small numbers that it is usually not demonstrable microscopically in pus or in stained sections. In experimentally inoculated mice, in contrast, the gram-positive oval or rod-shaped tissue forms of the organism occur in great numbers either free or in phagocytes (Fig. 240).

241). There is chronic inflammation, fibrosis, and epidermal hypertrophy.

Coccidioidomycosis.—This fungus disease occurs as primary pulmonary coccidioidomycosis and as progressive coccidioidomycosis (coccidioidal granuloma). The infection is endemic in the Far West and Southwest of the United States, but cases have also been reported from South America and from Italy. The infection is contracted by the inhalation of the fungus in dust. Rodents may serve as a reservoir.

The primary pulmonary form of the disease is benign and self-limited, and in

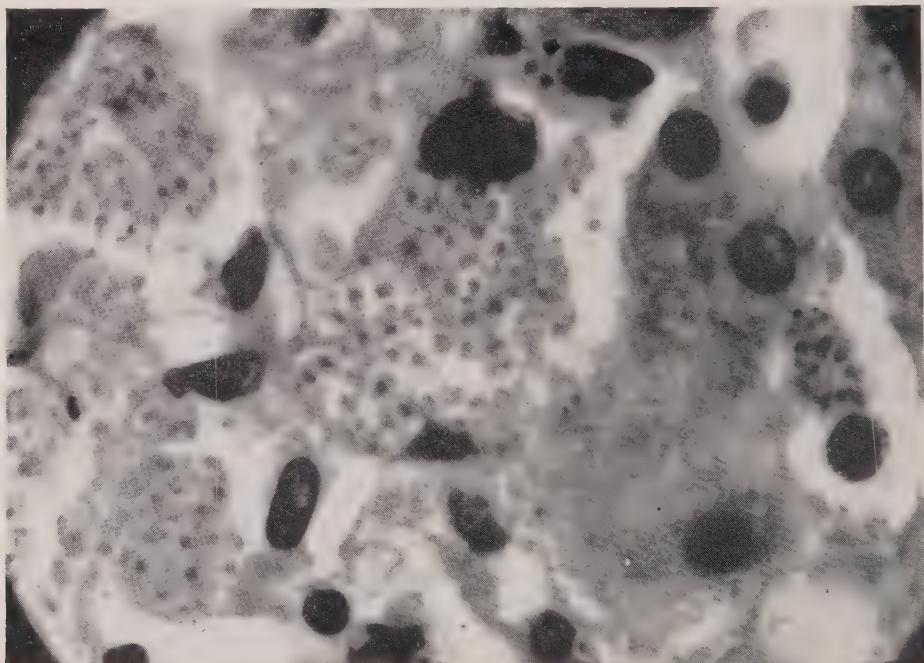


Fig. 236.—Histoplasmosis of the liver. Oval or round forms of *H. capsulatum* in the reticuloendothelial cells (Kupffer cells, macrophages).

The infection is chronic, lasting over a period of weeks or even years if untreated, but the lesions usually disappear gradually if iodides are taken orally by the patient. Generalized forms of sporotrichosis are very rare.

Chromoblastomycosis.—Like sporotrichosis, chromoblastomycosis is usually confined to an extremity, but it is more often the lower than the upper extremity. Chromoblastomycosis apparently begins from an infected wound. Warty nodules develop in the skin and subcutaneous tissues and may be present for many months or even years before the process extends beyond the foot. Microscopically the warty lesions are seen to contain brown, rounded septate organisms in giant cells or in minute abscesses (Fig.

many cases subclinical. Usually there is slight fever, called "valley fever," which terminates in one or two weeks. Organisms are present in the sputum. Roentgenograms indicate enlargement of the mediastinal lymph nodes, pneumonic consolidations, and bronchitis. Calcified nodules in the lung and in the draining lymph nodes may result, similar to the primary complex of tuberculosis. Fungus organisms have been demonstrated in these calcified lesions, but they are usually nonviable. In 3 per cent of the

cases, allergic manifestations develop a few days or weeks after the subsidence of the febrile period. These take the form of erythema nodosum or erythema multiforme. After recovering from primary pulmonary coccidioidomycosis the patient exhibits a positive skin test to the injection of coccidioidin. Seventy-seven per cent of those who have lived more than ten years in the San Joaquin Valley of California give positive coccidioidin tests.

Fig. 237.



Fig. 238.

Fig. 237.—Sporotrichosis of arm. Primary ulcer on back of wrist. Nodules on arm. (Photograph by courtesy of Dr. A. Gonzales Ochoa.)

Fig. 238.—Sporotrichosis of cheek with extension along lymphatics. (Photograph by courtesy of Dr. A. Gonzales Ochoa.)

Fig. 239.—Chronic inflammation in human sporotrichotic nodule. Giant cells and large and small mononuclear cells adjacent to area of necrosis. No organisms seen.

Fig. 240.—*Sporotrichum schenckii* in experimental sporotrichosis in a mouse. Gram stain.

Only a small number (0.2 per cent) of the patients with primary coccidioidomycosis develop progressive coccidioidomycosis. In this condition the infection becomes generalized, and nodules and abscesses (Fig. 243) form in the subcutaneous tissues, bones, viscera, and sometimes in the brain. The changes are

similar to those of generalized blastomycosis. The progressive form of coccidioidomycosis is fatal in about half the cases.

A primary cutaneous form of the disease occurs in addition to those forms already mentioned.

In the tissues the organism occurs as a rounded cell which may show homogeneous central material but which at a

Fig. 239.

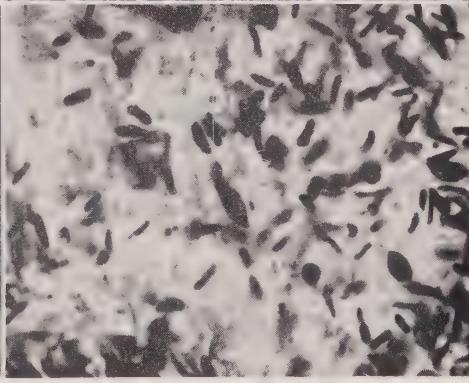
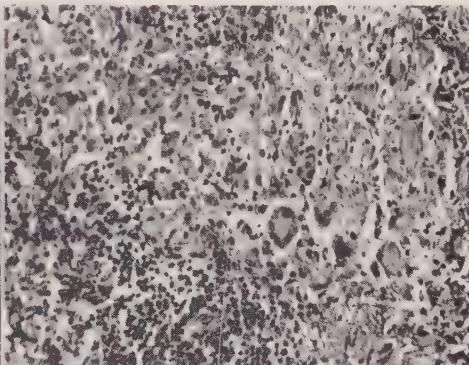


Fig. 240.

later stage may show many spores within the cell (endospores) (Figs. 244 and 245). These endospores burst through the cell wall and repeat the developmental process, known as endosporulation (Fig. 243). On artificial media at room temperature, hyphae develop to form a mycelium.

Rhinosporidiosis.—Rhinosporidiosis is thought to be a fungus infection because of the appearance of the organism in tissues, but the causative agent has never been grown in culture. The disease is endemic in India and Ceylon and sporadic in other parts of the world.

The nose is the common site of infection, though the pharynx and larynx, the eye, the skin, the ear, the genitalia, and the rectum may be infected. The nasal lesion develops as a polyp, or as polypoid masses, on the surface of which multiple minute white spots can be seen. These are relatively large sacs or spherules (200 to 300 microns in diameter) filled with spores (Fig. 242). The infecting spores, liberated when the spherule ruptures, are the size of red blood cells. They may incite tissue necrosis and abscess formation, but chronic inflammation and scarring are commonly noted when microscopic sections are examined.

in diabetics. *Candida albicans* can be isolated from the stools, skin, and sputum of many apparently normal persons.

The infection is usually one of surfaces, and deep infections are exceedingly rare. The organism grows as patches of grayish-white membrane on the mucous surfaces of the oral cavity, esophagus, or vagina (Fig. 246). The membrane consists of a tangled growth of gram-positive hyphae with spores produced at the junctions of segments (Fig. 247). The patch of "thrush" is thus a fungus mycelium. There is permeation and destruction of the epithelium of the mucous membrane, and bacterial growth is often associated with the fungus growth. Monilial vulvovaginitis is commonest in pregnant or in diabetic women.

On the skin, moniliasis may simulate infection with the dermatophytes. It often causes swelling

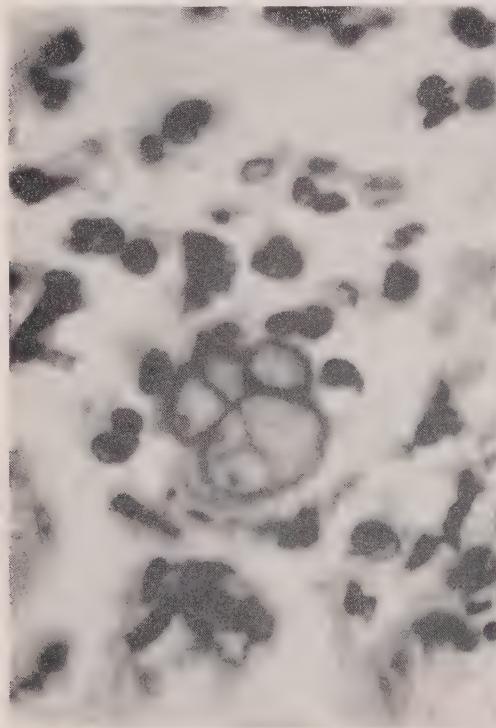


Fig. 241.

Fig. 241.—Chromoblastomycosis of skin. Septation of brown organisms is clearly shown, and neutrophiles surround them.

Fig. 242.—Rhinosporidiosis of nasal mucosa. of varying size. Additional spores elsewhere.



Fig. 242.

Fig. 242.—Rhinosporidiosis of nasal mucosa. Large sporangium containing numerous spores Chronic inflammatory response.

Rhinosporidiosis remains a localized infection and is seldom fatal. It may persist for several years and may disappear spontaneously in rare cases.

Moniliasis.—Moniliasis, often called thrush when it occurs on mucous membranes, is a fungus infection caused by species of *Candida*, usually *Candida albicans*. It has been reported from all parts of the world. It is more frequent

of the soft tissues about the nails (paronychia) and thickening of the nails, especially in persons whose hands are much in water. The cutaneous lesions may develop on the faces of infants and beneath the breasts of women. Generalized cutaneous moniliasis has been reported. In one fatal case of this sort, abscesses were present in the skin and subcutaneous tissues, and hyphae could be demonstrated in the abscesses.

In a recent case of a child observed by the writer, thrush was present on the tongue, buccal cavity, and face, together with soggy desquamating lesions between the toes and thickening of the toenails and thumbnails. Characteristic monilial filaments and spores were seen in sections of the nails, in potassium hydroxide preparations of the lesions on the skin and tongue, and *C. albicans* was grown from all these lesions.

Bronchopulmonary moniliasis is more frequently diagnosed clinically than it is encountered at autopsy. Certain shadows in roentgenograms of the lungs in connection with the demonstration of many organisms in the sputum suggest the diagnosis, and the diagnosis is strengthened by the clearing of the lungs in roentgenograms after treatment of the patient with iodides.

of their prevalence everywhere. It is important, therefore, not to ascribe etiological significance to species of *Aspergillus* which are cultivated from material taken from lesions of various sorts.

Aspergillosis is a rare human infection, involving lungs, paranasal sinuses, heart valves (endocarditis), and brain. Systemic infections have been recorded. Necrosis and suppuration may be produced. *Aspergillus* grows luxuriantly in the ear canal in otomycosis. Here the brown spores occur in "heads" at the summits of stalks.

When growth is in tissues, however, only hyphae are seen, as a rule.

Mucormycosis.—Mucormycosis is to be separated from most of the other fungus infections because *Mucor* is one of the Phycomycetes charac-

Fig. 244.

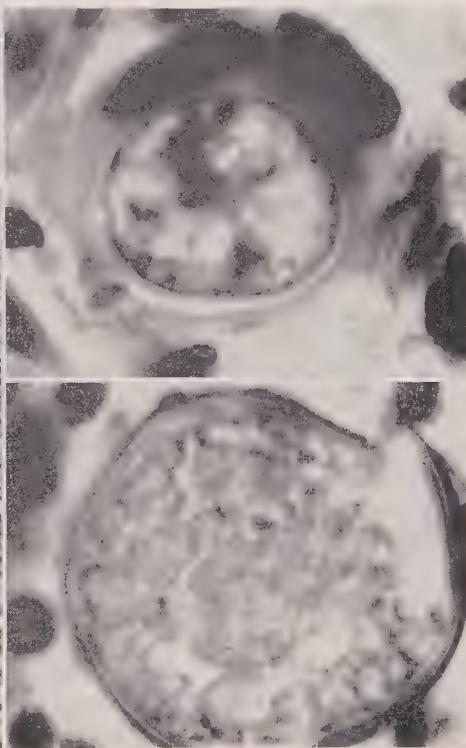


Fig. 245.

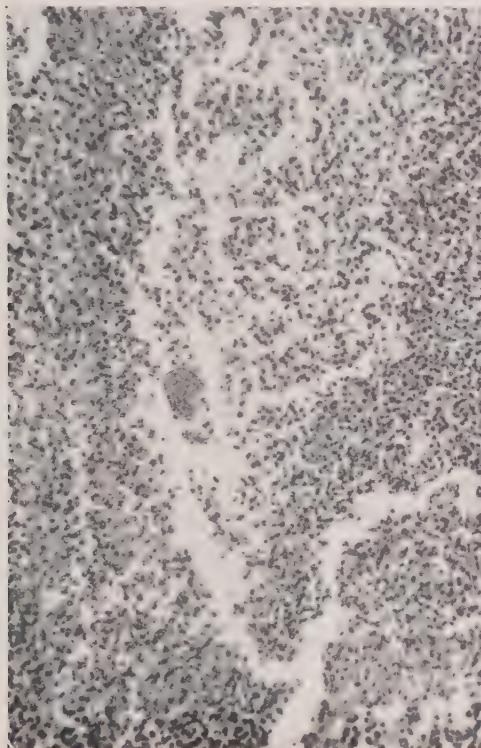


Fig. 243.

Fig. 243.—Ruptured spherule containing endospores. Abscess of lymph node. Progressive coccidioidomycosis (coccidioidal granuloma).

Fig. 244.—Young form of *Coccidioides immitis* in giant cell.

Fig. 245.—Endosporulating form of *Coccidioides immitis* with numerous endospores ready to escape.

Exceedingly rare deep infections may consist of infection of the meninges and ependyma of the brain.

Monilial endocarditis has been reported, usually in drug addicts who received heroin intravenously. The *Candida* in these cases was usually of a species other than *Candida albicans*.

Aspergillosis.—Species of *Aspergillus* are common contaminants of ulcers and wounds because

terized by a nonseptate mycelium, that is, by hyphae which are nonsegmented. The hyphae are usually much broader than those of other fungus infections. Several cases of cerebral mucormycosis have been reported in which the fatal infection developed a few days before death in diabetics, with spread from the nose or paranasal sinuses. The large hyphae were present in the walls of blood vessels and elsewhere in the cerebral tissue.

Polymorphonuclear response to the fungus was noted as well as areas of necrosis.

Maduromycosis.—Maduromycosis is restricted to those mycetomas caused by the true fungi. The majority of the mycetomas are caused by the false fungi, *Actinomyces bovis* and *Nocardia (Actinomyces) asteroides*. Maduromycosis is caused by a variety of fungi which are to be identified by mycologic cultural studies in conjunction with the appearance of the fungus in sections of tissues.

and contrast sharply with the tissues. White and orchid granules may occur. The type of fungus cannot be predicted accurately from the color of the granule. About the grain are pus cells and farther out macrophages, other chronic inflammatory cells, and scar tissue. Giant cells are seen at times in apposition with the grains.

The disease is chronic, lasting for years, and the lesions rarely heal spontaneously. The enlargement of the extremity and the drainage of pus cause trouble in walking and at times great

Fig. 246.

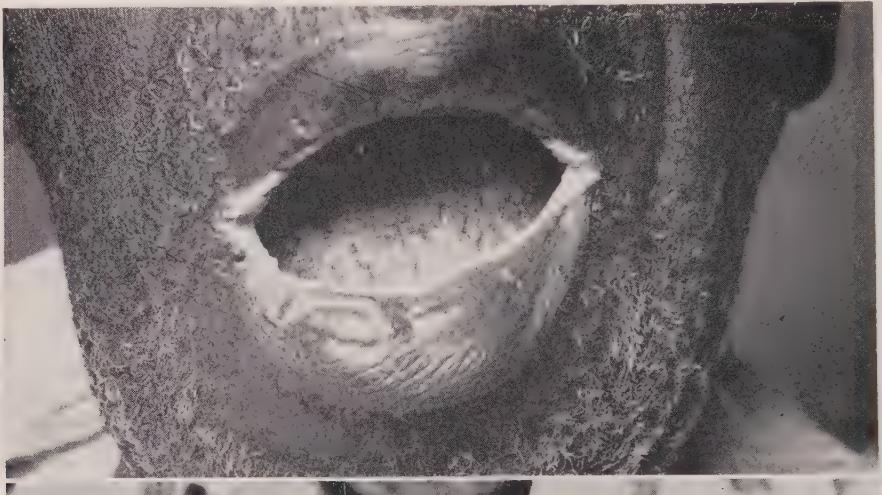


Fig. 246.

Fig. 246.—Moniliasis of lips and tongue.

Fig. 247.—*Candida albicans* from lesion of moniliasis. Growth is largely in filamentous form.

Maduromycosis caused by *Monosporium apiospermum* appears to be identifiable by the appearance of the grain in histopathologic sections, in the absence of cultural studies (Figs. 249 and 250). The central portion of the grain is made up of hyphae and the peripheral portion of spores. In maduromycosis the organisms are usually in the form of grains or granules, of various colors. Hyphae and spores are present in the grains, or sometimes only spores.

Mycetoma occurs in regions where the inhabitants go barefoot. The disease is more prevalent in the southern, and particularly in the southwestern, parts of the United States. The organism enters through the skin and comes from the soil.

The fungus granules are at times easily seen with the naked eye, especially when they are black

disability. Pain is not a prominent feature. There is danger to life from secondary infection by bacteria.

The Dermatomycoses or Tineas.—These superficial fungus infections are often spoken of as ringworm or "athlete's foot," although these lay designations may include infections caused by other fungi than those of the dermatophyte group, and even by bacteria. For example, *Candida albicans* can produce infections which are indistinguishable from those caused by the true dermatophytes: *Trichophyton*, *Microsporum*, and *Epidemophyton*.

The infections caused by the true dermatophytes may resemble one another closely. It is difficult to separate them on the basis of the generic etiological agent, and to use the terms trichophytosis, microsporosis, and epidermophytosis.



Fig. 247.

It is simpler to use an anatomic designation such as *tinea pedis*, *tinea cruris*, and the like. There is some correspondence between the etiological agent and the location of the clinical manifestation, for *Trichophyton* infects the hair, the skin, and the nails; *Microsporum* infects the hair and the skin; *Epidermophyton* infects the skin and the nails.

All of the dermatomycoses tend to be more severe and extensive in tropical climates. *Tinea pedis* or fungus infection of the skin of the feet is an astonishingly frequent and stubborn dermatomycosis. Males are afflicted more frequently than females, and adults more frequently than children. It is estimated that half of the population of the United States has it sooner or later. The total disability it causes is very great. It is often a chronic, essentially incurable, condition.



Fig. 248.—Maduromycosis (mycetoma) caused by *Cephalosporium*. (Photograph by courtesy of Dr. A. Gonzales Ochoa.)

The infection is apparently contracted indirectly from other people by exposure to the organisms on the floors of gymnasiums and baths. Those whose feet perspire easily seem predisposed to the disease, as the organism grows best in a moist environment. The disease is not especially contagious, as is indicated by the frequent lack of infection of all members of a family group even though one member carries the infection actively for years at a time. Sub-clinical infections occur as is indicated by the growing of the fungus at times from scrapings

from apparently normal skin. This constant harboring of organisms may be more important than exogenous reinfection in causing recurrences.

Fig. 249.

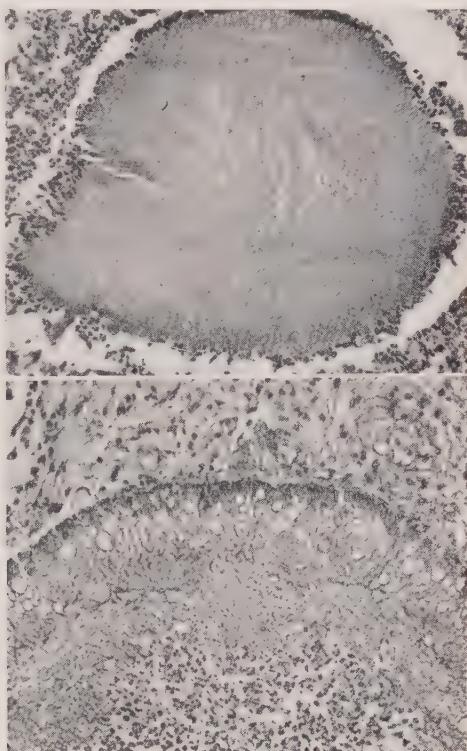


Fig. 250.

Fig. 249.—Grain of *M. apiospermum* surrounded by pus cells.

Fig. 250. Edge of grain of *M. apiospermum* to show spores.

Tinea pedis usually begins with the formation of fissures in the skin between the fourth and fifth toes. The infection is prone to extend to the soles of the feet and to the nails. Minute vesicles develop and are accompanied by severe itching and often by inflammation. These may enlarge and coalesce, forming large blebs beneath the skin. Deep fissures may cover the soles.

The organisms occur in the dead keratinized portion of the epidermis and nails, chains of spores, or more rarely hyphae, running parallel to the surface (Fig. 254). The vesicles are intraepidermal and organisms may sometimes be demonstrated in the wall of a vesicle. Inflammatory cells are numerous in the underlying dermis when the infection is active, but usually the organisms do not enter the dermis. Rupture of the vesicles may lead to secondary infections by streptococci. Cellulitis and lymphangitis may develop with redness of the lymphatic trunks extending up the leg. Tenderness and enlargement of the lymph nodes in the groin may follow. The secondary bacterial infections

constitute the most serious and incapacitating feature of tinea pedis. Pustular lesions may form. Hyperkeratosis and desquamation of the epidermis are often prominent.

Hypersensitivity to the fungus undoubtedly is responsible for sudden inflammatory recurrences. In addition, papular and vesicular lesions occurring on the hands concurrently with an attack of tinea pedis may be found to harbor no organisms, and are interpreted as evidences of hypersensitivity or allergy. The designation **dermatophytid** has been applied to such manifestations.

ulceration. **Tinea imbricata** is a similar infection which occurs in the tropics and is characterized by a striking pattern of concentrically arranged rings of papulosquamous patches sometimes involving the whole body. There is hyperkeratosis in the epidermis and mild chronic inflammation of the dermis.

In **tinea capititis** the scalp and hair are infected and scaly reddish patches are produced, often with loss of hair in smaller or larger areas of alopecia. Occasionally deep, ulcerative, chronic inflammatory lesions are present. When these arise on the bearded portions of the face,



Fig. 251.

Fig. 251.—Tinea corporis showing papular and scaling lesion of leg. Figs. 252 and 253 are from the same patient.

Fig. 252.—Tinea corporis of forearm.

Fig. 253.—Tinea corporis of arm.

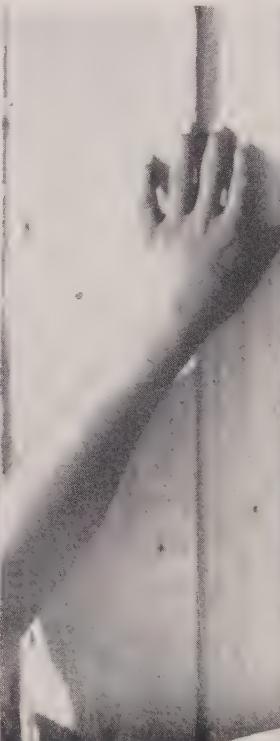


Fig. 252.



Fig. 253.

Infection of the nails, tinea unguium, or onychomycosis, produces thickening and brittleness of the nails. Onychomycosis may persist for decades.

In **tinea cruris** there are pruritic, red-brown patches or rings, with elevated borders, in the groins, periscrotal, perianal, and axillary regions.

In **tinea corporis** there is infection of the general body surface (Figs. 251, 252, and 253), and the lesions commonly are ring forms, which may coalesce. The peripheral portion consists of papules, while the central area clears. The lesions may extend into the skin and produce

the condition is spoken of as **tinea barbae** or **sycosis parasitica**. The hair in such areas may be brittle and lusterless because of the organisms growing in or about the hairs. When the infection involves the hair follicles, deep abscesses may form, with necrotic tissue and giant cells.

When **tinea capititis** is caused by a *Microsporum* from animal sources, the disease may disappear spontaneously, but when caused by dermatophytes from human sources **tinea capititis** may show no tendency toward spontaneous cure. In **tinea favosa** the scalp is usually affected, but other areas of the body may be involved also (Fig. 255). The characteristic feature of **tinea favosa**

is the presence of cup-shaped crusts which have a peculiar "mousy" odor. These are composed of fungi and necrotic cells.

METHODS OF STUDYING FUNGUS INFECTIONS

Lesions visible to the naked eye are studied by direct observation and description whether the subject is in the hospital ward or in the autopsy room. X-ray examination is of especial value in determining the presence of lesions in the lungs or in the bones. Fistulous tracts can sometimes be made visible if radiopaque liquids are introduced into them.

This naked eye visibility of the causative agent in the fungus diseases is like many of the parasitic, and unlike the bacterial and viral, diseases.

With the aid of the microscope the fungus is visible in pus, infected tissues, sputum, or spinal fluid in nearly all of the mycoses. For example, the filaments or spores of *Trichophyton gypseum* can be seen in scrapings from an infected, thickened toenail when the scrapings are treated with dilute solution of sodium hydroxide and heated to dissolve the keratinized material. When pus from a case of blastomycosis is examined directly, or diluted with tap water, or diluted and cleared with solution of sodium hydroxide, the round,

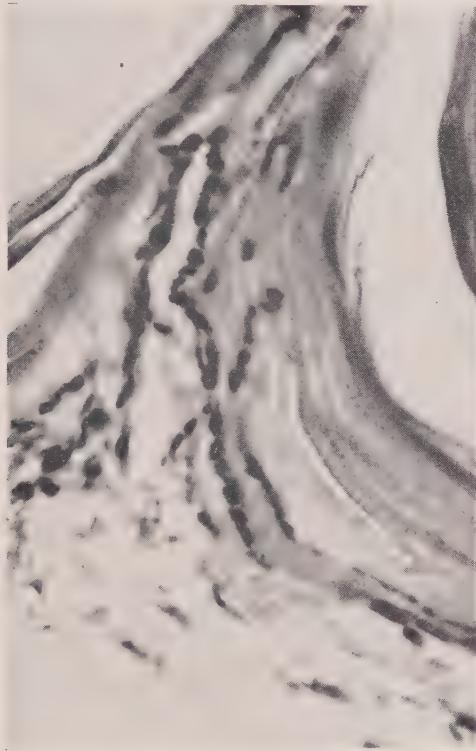


Fig. 254.

Fig. 254.—*Tinea unguium*. Chain of spores between lamellae of a toenail.
Fig. 255.—*Tinea favosa* of scalp of boy.

Sometimes the fungus itself is visible to the naked eye: as in otomycosis, in which *Aspergillus* may be seen in the ear canal; as in moniliasis, in which the white patches of thrush constitute a tangled mass of monilial filaments; as in actinomycosis and maduromycosis, in which the fungus colonies are seen in many cases as grains; and as in rhinosporidiosis, in which the large sporangia are visible on the surface of the nasal polyps. Moreover, in generalized blastomycosis the lesions may be constituted so largely of the fungus, essentially in pure culture, that the student must realize that he is looking at the fungus itself rather than at the host's reaction to the presence of the fungus (Fig. 235).



Fig. 255.

thick-walled, budding, tissue forms of *Blastomyces dermatitidis* may be observed.

This direct microscopic visibility of the infecting agent is of great practical importance in diagnosis. In some fungus infections, however, direct examination will not reveal the presence of the fungus. In lesions of sporotrichosis, in chronic tineas of the feet, in certain lesions of generalized blastomycosis, organisms may not be demonstrable. This is probably due to the death and disintegration of organisms or to the powerful effect of allergy.

The allergic and immunologic responses which characterize many of the fungus infections aid greatly in diagnosis.

The organism can be cultured with ease from many of the lesions. Material for culture should preferably be free from bacteria and should be planted both on Sabouraud's glucose agar to be maintained at room temperature and on blood agar to be incubated at 37° C. Cultures should be kept for a number of weeks before being discarded, since growth may be slow. Special cultural methods are necessary to identify certain of the fungi, while the identification of unusual fungi must be referred to the mycologist with special training in this branch of botany.

Because of the prevalence of fungi in the air, on the body surfaces, on mucous membranes, and on ulcerated lesions, it is important not to ascribe a causative role to every fungus grown from supposedly mycotic lesions. The demonstration of a fungus deep in a lesion accompanied by a characteristic inflammatory response is strong evidence of pathogenicity. Hence, histopathologic study may be essential in establishing a diagnosis.

Of the histopathologic methods for the study of fungi the ordinary hematoxylin and eosin staining is the most useful, and fungi are usually well seen by this method. The method of Gram is also useful since fungi are gram positive and hence are rendered more conspicuous. Mallory's aniline blue stain and silver impregnations demonstrate certain fungi effectively. Staining with periodic acid-Schiff's reagent and the method of Bauer gives excellent results.

Specific directions for the study and identification of pathogenic fungi are included in the third of the following general references.

References

General

- Baker, R. D.: The Histopathology of the Mycoses. Washington, D. C., 1945, Armed Forces Institute of Pathology.
 Baker, R. D.: Arch. Path. **44**: 459, 1947.
 Conant, N. F., Martin, D. S., Smith, D. T., Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia and London, 1944, W. B. Saunders Co.
 Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 3, Chicago, 1948, The Year Book Publishers, Inc.
 Moore, M., in Bercowitz, Z. T.: Clinical Tropical Medicine, New York, 1944, Paul B. Hoeber, Inc.

Actinomycosis and Nocardiosis

- Beamer, P. R., Reinhard, E. H., and Goodoff, M. D.: Am. Heart J. **29**: 99, 1945.
 Cope, Z.: Actinomycosis, London, 1938, Oxford University Press.
 Singer, J. J., and Ballon, H. C.: Am. Rev. Tuberc. **22**: 233, 1930 (streptotrichosis).
 Weed, L. A., and Baggenstoss, A. H.: Am. J. Clin. Path. **19**: 201, 1949.

Cryptococcosis (Torulosis)

- Cox, L. B., and Tolhurst, J. C.: Human Torulosis, Melbourne, 1946, Melbourne University Press.
 Freeman, W., and Weidman, F. D.: Arch. Neurol. & Psychiat. **9**: 589, 1923.
 Mider, G. B., Smith, F. D., and Bray, W. E.: Arch. Path. **48**: 102, 1947.

Mook, W. H., and Moore, M.: Arch. Dermat. & Syph. **33**: 951, 1936.
 Reeves, D. L., Butt, S. M., and Hammack, R. W.: Arch. Int. Med. **68**: 57, 1941.

Blastomycosis (North American)

- Baker, R. D.: Am. J. Path. **18**: 479, 1942.
 Martin, D. S., and Smith, D. T.: Am. Rev. Tuberc. **39**: 275, 488, 1939.
 Stober, A. M.: Arch. Int. Med. **13**: 509, 1914.

South American Blastomycosis

- Almeida, F. de: Mycologia Medica, São Paulo, Brazil, 1939.
 Cunha Motta, L.: Am. J. Path. **24**: 323, 1948.
 Moore, M.: Arch. Dermat. & Syph. **38**: 163, 1938.

Histoplasmosis

- Anderson, W. A. D., Michelson, I. D., and Dunn, T. M.: Am. J. Clin. Path. **11**: 344, 1941.
 Beadenkopf, W. G., and Loosli, C. G.: J. A. M. A. **146**: 621, 1951.
 Darling, S. T.: Arch. Int. Med. **2**: 107, 1908.
 Henderson, R. G., Pinkerton, H., and Moore, L. T.: J. A. M. A. **118**: 885, 1942.
 Parson, R. J., and Zarafonetis, C. J. D.: Arch. Int. Med. **75**: 1, 1945.
 Weed, L. A., and Parkhill, E. M.: Am. J. Clin. Path. **18**: 130, 1948.

Sporotrichosis

- Gastineau, F. M., Spolyar, L. W., and Haynes, E.: J. A. M. A. **117**: 1074, 1941.
 Schenck, R. B.: Bull. Johns Hopkins Hosp. **9**: 286, 1898.

Chromoblastomycosis

- Martin, D. S., Baker, R. D., and Conant, N. F.: Am. J. Trop. Med. **16**: 593, 1936.
 Moore, M., Cooper, Z. K., and Weiss, R. S.: J. A. M. A. **122**: 1237, 1943.
 Simpson, F. W., Harington, C., and Barnetson, J.: J. Path. & Bact. **55**: 191, 1943.

Coccidioidomycosis

- Aronson, J. D., Saylor, R. M., and Parr, E. I.: Arch. Path. **34**: 31, 1942.
 Butt, E. M., and Hoffman, A. M.: Am. J. Path. **21**: 485, 1945.
 Caldwell, G. T.: Texas State J. Med. **38**: 376, 1942.
 Cox, A. J., and Smith, C. E.: Arch. Path. **27**: 717, 1939.
 Dickson, E. C.: J. A. M. A. **111**: 1362, 1938.
 Forbus, W. D., and Bestebeurte, A. M.: Mil. Surgeon **99**: 653, 1946.
 Jacobson, H. P.: Fungus Diseases, Springfield, Ill., 1932, Charles C Thomas.

Rhinosporidiosis

- Caldwell, G. T., and Roberts, J. D.: J. A. M. A. **110**: 1641, 1938.
 Weller, C. V., and Riker, A. D.: Am. J. Path. **6**: 721, 1930.

Moniliasis

- Gausewitz, P. L., Jones, F. S., and Worley, G., Jr.: Am. J. Clin. Path. **21**: 41, 1951.
 Halpert, B., and Wilkins, H.: J. A. M. A. **130**: 932, 1946.
 Miale, J. B.: Arch. Path. **35**: 427, 1943.
 Wikler, Abraham, and others: J. A. M. A. **119**: 333, 1942.

Aspergillosis

- Cawley, E. P.: Arch. Int. Med. **80**: 423, 1947.
 Cooper, N. S.: Arch. Path. **42**: 644, 1946.
 Zimmerman, L. E.: Arch. Path. **50**: 591, 1950.

Mucormycosis

- Gregory, J. E., Golden, A., and Haymaker, W.: Bull. Johns Hopkins Hosp. **73**: 405, 1943.
Le Compte, P. M., and Meissner, W. A.: Am. J. Path. **23**: 673, 1947.

Mycetoma

- Burns, E. L., Moss, E. S., and Brueck, J. W.: Am. J. Clin. Path. **15**: 35, 1945.
Gammel, J. A.: Arch. Dermat. & Syph. **15**: 241, 1927.
Shaw, R. M., and MacGregor, J. W.: Canad. M. A. J. **33**: 23, 1935.
Thompson, H. L.: Arch. Surg. **16**: 774, 1928.

Dermatomycoses

- Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, vol. 11, Berlin, 1928, Julius Springer.
Montgomery, R. M., and Casper, E. A.: J. A. M. A. **128**: 77, 1945.
Pardo-Castello, V.: Diseases of the Nails, Springfield, Ill., 1936, Charles C Thomas.
Sabouraud, R.: Les Teignes, Paris, 1910, Masson et Cie.
Sulzberger, N. B., Baer, R. L., and Hecht, R.: Arch. Dermat. & Syph. **45**: 670, 1942.

Staining Methods

- Lillie, R. D.: J. Lab. & Clin. Med. **32**: 76, 1947.

Chapter 16

PROTOZOAL AND HELMINTHIC INFECTIONS

ENRIQUE KOPPISCH

PROTOZOAL DISEASES

Amebiasis

Etiology.—*Endamoeba histolytica* is found in the feces as trophozoites, or vegetative amebae, and as precystic and cystic forms. The trophozoites are seen in diarrheal stools and the cysts in formed feces. Only the trophozoites occur in tissues. In unstained preparations they average 18 to 30 microns in diameter. The nucleus is usually invisible, but may appear as a delicate ring of minute chromatin granules, while the ectoplasm forms a clear peripheral zone about the more opaque and finely granular endoplasm. In warm, freshly passed feces the amebae show active formation of pseudopodia. They frequently contain vacuoles and engulfed erythrocytes, the latter being of importance in differentiating from the very similar but harmless *Endamoeba coli*. In preparation for encystment the pseudopodia become blunt and sluggish, and the ameba rounds out into the *precystic form*. The *cysts* are hyaline, spherical, and have a refractile wall; they range in diameter from 5 to 20 microns. The cytoplasm is finely granular and clear, and contains 1 to 4 nuclei that are either invisible in unstained preparations, or small and refractile. For exact identification of this ameba, fixed fecal smears stained with iron hematoxylin may be necessary to bring out the characteristic nuclear structure in cysts and trophozoites.

Epidemiology and Transmission.—Amebiasis occurs throughout both temperate and tropical countries, but is more prevalent in the latter where individual infections are apt to be more severe. It is estimated that the general incidence in the United States is 10 per cent, but in the great majority of these the condition is asymptomatic. The infection is usually acquired by the ingestion of food or water contaminated with human excreta containing cysts of *E. histolytica*. The more common means of pollution of food are the house fly and the soiled fingers of cooks and other food-handlers who are cyst-passers. In some parts of the world an important source of infection is the use of human dejecta for the fertilization of vegetable gardens. Defective plumbing has resulted in important outbreaks of amebic dysentery through the contamination of the water supply with sewage. Amebiasis is more prevalent in rural than in urban communities. It is more frequent in males than in females, and has the highest incidence in the age group 26 to 30. It is rare before 5 years of age.

Pathogenesis and Pathologic Anatomy.—After ingestion of cysts, excystment takes place in

the alkaline contents of the small intestine with the formation of four amebulae from each cyst. Once in the colon, these grow to the adult (trophozoite) stage, and there maintain themselves for many years. It is still unsettled whether the amebae are able to live in the lumen indefinitely without producing lesions of the colonic mucosa, but the general opinion is that lesions are always produced. Not infrequently, however, ulcers are present without diarrhea or other important symptoms, or the clinical manifestations may be vague and not characteristic.

Colitis is the basic pathologic feature of amebiasis, but it is frequently complicated by amebic liver abscess. In very acute cases the whole colon may be affected from cecum to rectum, and the process may even extend to the distal portion of the ileum. The sites of preference, however, are the cecum and ascending colon, followed by the sigmoid and rectum.² The cardinal clinical manifestation of acute amebic colitis is dysentery, or the frequent passage of bloody stools accompanied by pain and tenesmus. Since this depends on involvement of the rectum, which is found not in all but in about 70 per cent of cases at autopsy, the sign is lacking in a significant number of the patients.

The earliest stages of invasion of the colonic mucosa by the amebae are practically unknown in man. In experimental amebiasis of the dog and monkey this begins with the active multiplication of amebae and the formation of colonies on the intestinal epithelium. They then penetrate by means of their ameboid motion,³ probably aided by some lytic enzyme that they elaborate.⁴ Invasion usually takes place between the glands of Lieberkühn, and the amebae advance through the tunica propria as far as the muscularis mucosae, by which they are temporarily detained. Usually the glands are invaded by penetration across the basement membrane. At first there is little or no tissue reaction to the presence of amebae; soon, however, the invaded locus becomes edematous and necrosis occurs, while the surrounding blood vessels engorge and the lymphatics dilate. A few lymphocytes and monocytes infiltrate the area of necrosis. These early lesions are multiple, and are visible grossly as minute, gray or yellow points surrounded by a narrow red zone.

Once in the submucosa, the amebae extend more laterally in this layer than deeply. The above minute points of necrosis, therefore, expand into flask-shaped excavations involving

small portions of the mucosa and larger ones of the submucosa. These cavities contain glairy plugs of yellowish or brownish, mucopurulent exudate in which numerous amebae are present. Grossly they appear as rounded, projecting, congested nodules having a minute opening on top and averaging 5 mm. in diameter. By extension of the necrosis, always more advanced in the submucosa, the typical amebic ulcers develop. At first these follow the crests of the valvulae, and thus are transversely placed, but soon they become round or oval. They vary in diameter from a few millimeters to about 10 cm., and have swollen, red, and undermined borders. The base is yellow when covered by fibrinopurulent exudate, greenish when bile-stained, or red or brown from hemorrhage. These ulcers may reach any depth, but usually extend no deeper than the muscle coat. In severe cases they coalesce, yet undermined bridges of mucosa remain here and there, and later become detached at one end, forming dependent tags of tissue. In these cases gangrene may supervene, and then the mucosal aspect is very dark brown or black and covered by shreds of necrotic tissue and exudate. The edema of the submucosa often produces a marked thickening of the wall of the colon in the involved portions.

larger ulcers, healing may result in deformity and contracture of the intestinal lumen. Fibrous adhesions of the colon to segments of small intestine are a frequent sequel of amebic colitis.

The microscopic picture is characterized by necrosis of the mucosa and submucosa with ulceration (Fig. 257), the process being more advanced in the submucosa. About the lesions there is marked edema, particularly of the latter coat, and a relatively scanty infiltration with lymphocytes, monocytes, and plasma cells. Polymorphonuclears are not present, except when secondary bacterial infection supervenes. In the base of the ulcers the blood vessels are congested and the smaller ones undergo thrombosis. The necrosis is due to the direct effect of the amebae, and in part to thrombosis of blood vessels and to undermining with interference of the blood supply. The amebae (Fig. 258) are usually found over extensive portions of the submucosa in the neighborhood of the lesions. They extend about blood vessels into the muscle coat and even reach the subserosa. There is early invasion of lymphatics and venules, where they may be found in large numbers, yet their passage to regional lymph nodes is very rare. In ordinary sections stained with hematoxylin and eosin they stand out



Fig. 256.—Amebic colitis. Extensive, undermined ulcers covered in places by a black slough; intervening mucosa but little altered, except for swelling. (Tissue by courtesy of Dr. James T. Culbertson.)

Besides the flask-shaped ulcers and the larger undermined ones, another characteristic feature is the normal appearance of the mucosa away from the amebic lesions and in the uninvolved segments (Fig. 256). When the ulcers are close together, however, the mucosa is swollen and congested. Amebic ulcers may give rise to hemorrhage, and they may perforate and produce either generalized peritonitis or an abscess. Amebae may wander into the peritoneal cavity and instigate the formation of a pale fibrinous exudate, poor in leukocytes. Some ulcers heal without leaving a trace when small, or they leave depressed scars. In the case of

prominently because of their size of about 25 microns, the sharply defined round nucleus, and the fine vacuoles and occasional erythrocytes in their cytoplasm.

Complications.—

AMEBIC ABSCESS OF LIVER.—The incidence of amebic liver abscess, as found at autopsy in cases of amebic dysentery, is about 40 per cent.³ It is very rare in children, and about one-tenth as frequent in women as in men.¹¹ The right lobe is involved in 50 to 68 per cent. In about 40 per cent of the cases there are two or three abscesses, rather than a solitary one (Fig. 259).

The usual aspect of a fully developed solitary abscess is that of a cavity, 8 to 12 cm. in diameter, situated close to the dome of the right lobe, or near the undersurface and hepatic flexure of the colon. The contents, frequently likened to anchovy sauce, are thick and grumous, yellowish-red or chocolate-colored, and contain recognizable shreds of necrotic liver tissue. When contaminated with bacteria, they are purulent. The inner aspect of the abscess is soft, very ragged, yellowish or brown, and surrounded by compressed

liver tissue or by a pale zone of fibrosis. Microscopically, the inner aspect is composed of softened hepatic tissue that has undergone coagulation necrosis. This is surrounded by liver parenchyma that is being replaced by fibrous tissue and which is infiltrated with lymphocytes and plasma cells. The amebae are found a little below the innermost layers of the zone of necrosis, and are rarely demonstrable in the necrotic contents, at operation or postmortem examination. In most cases the liver is enlarged to about 2,500

Fig. 257.

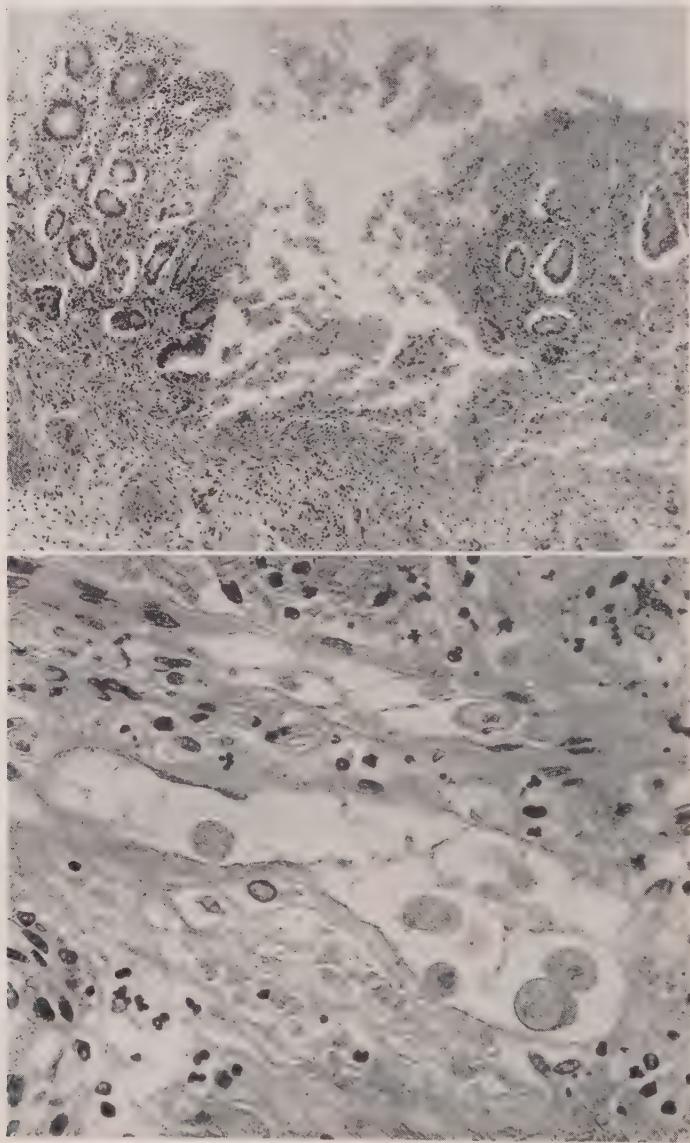


Fig. 258.

Fig. 257.—Amebic colitis. Very early ulcer with beginning undermining to the right. ($\times 800$.)
Fig. 258.—Amebic colitis. Amebae within lymphatic and in tissues of submucosa; scant infiltration with neutrophiles and lymphocytes. ($\times 360$.)

grams and presents extensive, diffuse fibrosis and round-celled infiltration of the portal spaces, as well as generalized centrilobular necrosis.

Liver abscesses begin as dark, wedge-shaped areas in which there are isolated and conglomerate points and nodules measuring up to 0.5 cm. in diameter. The wedge-shaped areas represent zones of hepatic necrosis originating about segments of the portal veins in which the amebae have provoked thrombosis; ultimately, there is softening and liquefaction of the whole zone.^{9, 10} The amebae are transported from the colon with the venous blood.

Amebic liver abscesses may rupture into neighboring organs or cavities. Rupture occurs most frequently into the right pleural cavity (37 per cent), right lung (25 per cent), and pericardial sac (19 per cent), followed in decreasing order of frequency by rupture into the stomach, lumbar region, colon, inferior vena cava, right kidney, bile ducts, and duodenum.³ The abscess may obstruct the pylorus or duodenum by compression.

frequently, through the bronchi, a cavity is formed. Both the contents and the cavity have a close resemblance to those of amebic liver abscess. Most or all of the lower lobe undergoes consolidation. Microscopically, there is an inner zone of necrotic pulmonary tissue and about this the alveolar septa show marked broadening by interstitial fibrosis. The alveoli are small, lined with cuboidal epithelium, and filled with vacuolated macrophages, lymphocytes, and occasional plugs of fibrin. The amebae are found about the necrotic zone and may enter bronchi and thus appear in the sputum. In some cases the pulmonary abscess arises by dislodgment of thrombi containing amebae in branches of the hepatic vein. In still other cases amebae have been transported in the blood from colonic lesions. Amebic bronchitis without abscess of the lung has been described clinically but the condition has not been encountered at autopsy.



Fig. 259.—Multiple amebic abscesses of the liver. (AFIP No. 1058-3.)

The abscess usually develops about one month after onset of acute amebic colitis, but may occur concomitantly with it or much later. Amebic ulcers of the colon are found in most cases at autopsy, but in some the colonic lesions are totally healed or inconspicuous. An abscess may develop in asymptomatic carriers.

AMEBIC ABSCESS OF LUNG.—The proximity of many amebic abscesses of the liver to the dome leads to the formation of fibrous adhesions between that organ and the diaphragm, and between the latter and the base of the right lung. With an extension of the hepatic process, amebae may migrate directly to the lung, where they first produce a focal pneumonic consolidation. This is soon followed by necrosis and softening, as in the liver. With discharge of the necrotic tissues into the pleural space or, more

AMEBIC ABSCESS OF BRAIN.—In the brain an amebic abscess is usually solitary, and may be situated in any part of either cerebral hemisphere; the cerebellum is rarely involved. According to Armitage,¹ amebae are transported with the blood to the leptomeninges, where an inflammatory focus first develops. From here they are carried in the lymphatics or arterioles to the depths of the brain, where, much as in the liver, they produce a focus of necrosis and encephalomalacia with relatively little inflammation, unless contaminated with pyogenic bacteria. The contents resemble those of an amebic liver abscess. The wall, inwardly, may be composed of irregularly intercommunicating cavities, about which the neural tissue is necrotic and undergoing lysis; farther out there is congestion, some glial proliferation, and some infiltration with lymphocytes.

These abscesses may reach a diameter of 10 cm. They usually arise concomitantly with liver abscess or shortly thereafter, and are fatal within one or two weeks of their clinical onset. Only 61 cases have been reported, and of these five were not accompanied by amebic abscess of the liver or lung.⁵ In the latter cases the amebae probably were transported in the circulation from lesions in the colon.

AMEBIASIS OF SKIN.—*E. histolytica* may rarely produce cutaneous ulcers with a discharge that is usually offensive and like anchovy sauce. The base is composed of partly necrotic granulation tissue densely infiltrated with polymorphonuclears. The surrounding tissue shows fibrosis and lymphocytic and plasma cell infiltration. Amebae are present in the tissues of the base and in the exudate. Amebic skin ulcers develop under the following circumstances: (a) in the borders of surgical incisions for drainage of an amebic ulcer, or for appendectomy and colostomy, (b) in the margin of the skin wound in spontaneous rupture of a liver abscess through the abdominal wall, (c) very rarely, in the glans penis, from sexual contact per rectum, and (d) perianally or perivulvally from self-contamination.

AMEBIC GRANULOMA OF COLON.—This lesion consists of a localized and massive inflammatory thickening of the wall of the colon. It is secondary to amebic ulceration, and easy to mistake clinically for carcinoma. The remainder of the colon usually shows no amebic involvement. The cecum, hepatic and splenic flexures, and the sigmoid colon are the more frequent seats of this lesion. It appears as a dense mass surrounded by fibrous adhesions. On section the mass is pale, finely fibrillary, dense in portions and edematous in others. Microscopically it is composed of fibrous tissue, edematous in places, and infiltrated with eosinophiles, plasma cells, and lymphocytes; the last-named form prominent and compact groups. The amebae are found in the necrotic base of the ulcer, and a few extend a little more deeply, but not to the fibrous mass itself.

There are a few cases on record of cystitis, pyelitis, cervicitis, and vaginitis, and of splenic, renal, or perinephric abscess due to *E. histolytica*, but these complications are exceedingly rare, and a few of them lack complete verification.

Immunity.—No race is immune to amebiasis. Yet, since the colonic lesions and abscesses of the liver may show reactive fibrosis, and some of the former may even heal, there is no doubt that a certain amount of immunity, at least local, develops among the infected. This is limited and never very effective, of itself, once the amebic lesions are well developed. As far as is known, amebiasis, even in the absence of signs and symptoms, is not self-limited, nor does it tend to disappear without treatment. That immune bodies do develop is shown by Craig's work on the complement fixation test, which is positive in 70 per cent of all cases, symptomatic or not, but which is not yet practical for application as a laboratory procedure.

African Trypanosomiasis

Introduction.—The protozoa of the family *Trypanosomatidae* may be found in invertebrate

hosts only, or else require, as part of their life cycle, both invertebrate and vertebrate hosts. Those pathogenic to man require an insect vector. Four different stages may be necessary for completion of the life cycle, each one corresponding to the following distinct forms of the parasite: leishmania, leptomonas, crithidia, and trypanosome. The simplest is the leishmania, a round or oval organism measuring 2 to 5 microns in diameter. It has a spherical or ovoid nucleus and a rodlike or dotlike kinetoplast. A delicate red filament, the rhizoplast, extends from the latter to the cell membrane, and represents the root of the flagellum, which in this form never becomes free. The African trypanosomes pathogenic to man have no leishmanial stage. In leptomonas, crithidia, and trypanosomes the cell body is spindle-shaped, the nucleus is central or nearly so, and a single flagellum extends from the anterior end. The main distinction between these three forms lies in the position of the kinetoplast, from which the flagellum arises. Thus, in leptomonas the kinetoplast is at the anterior end, and the flagellum emerges directly, without an undulating membrane. In crithidia the kinetoplast is just anterior to the nucleus, and the flagellum runs along the free margin of an undulating membrane that extends half the length of the organism. In trypanosomes, since the kinetoplast is at the posterior end of the body, the flagellum and undulating membrane are correspondingly longer.

A typical trypanosome has a graceful, undulant, spindle-shaped body 15 to 30 microns in length and 1.5 to 3 microns in width. In Romanowsky-stained films the cytoplasm and undulating membrane are pale blue; the former may contain dark blue volutin granules. The nucleus (trophonucleus) is red to purple, and has a large karyosome. The kinetoplast is ordinarily seen as a dark red dot in the blunt posterior end of the trypanosome, but in reality is composed of an oval parabasal body and a dotlike blepharoplast. The flagellum is red, and extends from the blepharoplast, along the free margin of the undulating membrane, to become free at the pointed anterior end of the parasite.

Of six genera in the family *Trypanosomatidae*, only two are of importance to the student of human pathology: *Trypanosoma* and *Leishmania*. Three species of each of these are the cause of the important diseases listed below.

PARASITE	DISEASE
<i>Trypanosoma gambiense</i>	Gambian or Mid-African sleeping sickness
<i>Trypanosoma rhodesiense</i>	Rhodesian or East African sleeping sickness
<i>Trypanosoma cruzi</i>	Chagas' disease or American trypanosomiasis
<i>Leishmania donovani</i>	Kala-azar or visceral leishmaniasis
<i>Leishmania tropica</i>	Oriental sore or cutaneous leishmaniasis
<i>Leishmania brasiliensis</i>	South American or mucocutaneous leishmaniasis

Gambian trypanosomiasis is transmitted by the bite of the tsetse fly *Glossina palpalis*, and by *G. tachinoides* to a lesser extent. The principal vector of the Rhodesian form is *Glossina mors-*

tans, with *G. swynnertoni* acting in this capacity in some regions. On biting a patient, these flies ingest trypanosomes with the blood. These multiply in the midgut, pass upwards to the buccal cavity, and then to the salivary glands, where they revert to the crithidial stage. After further multiplication in the salivary glands, young metacyclic trypanosomes develop, these being the infective form introduced into man by the bite of the fly. The cycle in the insect requires an average of twenty days.

Man is the main reservoir of both diseases, yet there is strong evidence indicating that wild game, especially several species of antelope, and some domestic animals (pigs, cattle, goats, and sheep) may also serve in that capacity. The main requisites for dissemination of African trypanosomiasis are the presence of infected human beings and tsetse flies in regions where the temperature is high enough (23° to 29° C., or 75° to 85° F.) to allow for cyclical development of the trypanosomes in the latter. These flies feed readily on man when he enters the jungle or allows the bush to grow close to his habitation. The highest incidence of the disease is in young adults.

GAMBIAN TRYPANOSOMIASIS

(MID-AFRICAN SLEEPING SICKNESS)

Pathogenesis and Pathologic Anatomy.—In both Gambian and Rhodesian trypanosomiasis the cases can be grouped clinically as follows: (1) those with a chronic course of several years' duration and few or no evidences of the disease, except for changes in the cerebrospinal fluid; (2) cases with a well-defined early stage characterized by fever, enlarged lymph glands, tachycardia, exanthematous eruptions, and transient edemas, a late encephalitic stage, and a course of over one year; and (3) cases with a very acute course culminating in death within a few months, usually without symptoms of encephalitis. The distinction between the two forms of the disease lies in that most cases of the Gambian fall in the first category, and most cases of the Rhodesian in the third.^{19, 22}

Pathologically the disease is characterized by a chronic meningoencephalomyelitis and chronic lymphadenitis. It also seems that myocarditis is an important part of the disease during the early stage.^{20, 23, 26}

The brain may look normal grossly. The more frequent alterations are opacity and thickening of the leptomeninges over the dome, the presence of patchy areas of adhesion to the dura mater, and an increased amount of cerebrospinal fluid, which is either clear or faintly turbid and yellowish. The cerebral sulci may be shallow and the gyri broadened. Externally and on section, congestion and minute hemorrhages may be visible, but extensive hemorrhage is only rarely encountered. Microscopically, the main change is a dense and diffuse infiltration of the pia-arachnoid, and about the cerebral blood vessels, with lymphocytes, plasma cells, monocytes, and macrophages. The infiltration extends over the cerebral and cerebellar surfaces, into the sulci, and over the spinal cord. The dura mater often is similarly involved. The perivascular collections appear as prominent cuffs throughout the

cerebrum, basal ganglia, medulla, and cerebellum. In some cases they are more marked in the deeper cortical layers; in others, in the white matter. The cell collections about blood vessels are sharply outlined, because they are contained within the Virchow-Robin spaces. The endothelial cells lining some capillaries become swollen, which, together with the marked perivascular infiltration, at times leads to narrowing of the lumen and the formation of small foci of encephalomalacia. Wherever the cellular infiltrations occur, there are usually found, in variable numbers, the so-called "morula cells" of Mott. These are spherical, 3 to 12 microns in main diameter, and are characterized by a dark-staining eccentric nucleus and by the presence in their cytoplasm of spherical or faceted, eosinophilic, hyaline bodies. They probably represent degenerate plasma cells of the type of Russell's acid fuchsin bodies, although some authors believe them to be of neuroglial origin. Though not pathognomonic, they are fairly characteristic of the disease.

The neurons usually show no change, but in the more severe and older infections may undergo acute swelling, becoming enlarged and globular, while the Nissl granules are diminished in number, or disappear altogether (chromatolysis). There may be neuronal atrophy and spherulosis. These alterations affect the cerebral and cerebellar cortex, the basal nuclei, and Ammon's horn. Occasional Purkinje cells of the cerebellum are similarly affected.¹⁵

The neuroglial alterations are of irregular and variable distribution, and appear to depend on obstruction of capillaries for their inception. They occur most frequently deep in the cortex and in the white matter, and consist mainly of hypertrophy of the fibrous astrocytes. In the superficial parts of the cortex some gliosis takes place when the overlying pia-arachnoid is strongly inflamed, but never to the extent present in general paralysis. The oligodendroglia in the vicinity of perivascular cuffs shows degenerative signs, mainly in the form of swelling. The microglial cells of the cortex become greatly increased in number and form very long "rod cells" arranged perpendicularly to the surface.

The choroid plexus of the fourth ventricle shows edema, round-cell infiltration, and fibrosis, producing partial obstruction of the foramina of Luschka.²¹ This explains the slight dilatation of the ventricles observed in some cases.

The spinal cord presents changes of the same kind as the brain, but much less pronounced. In addition, there is multiplication of ependymal cells lining the central canal, and glial proliferations may extend into the lumen. Degeneration of medullated fibers is usually demonstrable, particularly in the posterior columns. The cells of Clarke's column (*nucleus dorsalis*) have been said to undergo degenerative changes in most cases, and there is infiltration of the spinal ganglia with lymphocytes and plasma cells.

The enlargement of lymph glands may be localized or generalized, usually being most prominent in the posterior cervical triangles (Winterbottom's sign), but frequently affecting the axillary and inguinal groups as well.

In the early febrile stage the glands are soft, discrete, and have a pink, congested cut surface. Microscopically there is hyperplasia of the lymphoid tissue and, to a lesser extent, of the reticulum cells, together with infiltration by plasma cells. The littoral cells enlarge and mobilize into the sinuses. Trypanosomes are usually numerous in the lymph nodes at this stage. In the final lethargic phase the lymph nodes are small and firm; the capsule is thickened. The microscopic picture is one of increased prominence and fibrosis of the reticulum. At this stage trypanosomes are scarce or altogether absent.

The cerebrospinal fluid undergoes alterations of great diagnostic and prognostic importance. Increased numbers of plasma cells and lymphocytes, increased albumin, diminution of glucose and chlorides, and the occasional presence of trypanosomes are the main features.

RHODESIAN TRYPANOSOMIASIS

(EAST AFRICAN SLEEPING SICKNESS)

There are no fundamental differences in the morbid anatomy between Gambian and Rhodesian trypanosomiasis, except that because of the more acute course, changes in the central nervous system are apt to be less well developed in the untreated Rhodesian type. The effect of treatment on the pathologic picture is well shown by Calwell's study¹⁶ of seventeen brains. He found the same alterations in that organ as have been described for the Gambian form, apparently due to "treatment insufficient to cure but sufficient to prolong life for even several years."

Hawking and Greenfield's study¹⁸ of two cases, uncomplicated by treatment, is important because of the scarcity of such reports. They found extensive peritoneal, pleural, and pericardial effusions of clear or light yellow fluid containing numerous trypanosomes. The heart was small in both, soft in one. Microscopically, extensive epicardial, myocardial, and, to a much lesser extent, endocardial infiltration was found. Lymphocytes predominated, but macrophages, plasma cells, and polymorphonuclears also abounded. There was no fibrin on the epicardium. The myocardial infiltration was both diffuse and focal. There were groups of shrunken and disintegrating muscle fibers. In one case the cell infiltration was less marked than above, macrophages predominated in the epicardium, and the interstitial tissue of the myocardium was much increased. The brain was normal grossly in both. Microscopically, the main feature was fairly marked meningitis in patches (mainly macrophages, with lesser numbers of plasma cells and lymphocytes) over the cerebrum, cerebellum, and upper cervical cord. In the sulci the cell infiltration was not diffuse but focal. Perivascular infiltrations in the nerve tissues were seen only near the leptomeninges and beneath the ependyma of the third ventricle, but were scanty and inconspicuous.

It thus seems that in untreated Rhodesian sleeping sickness, not only are the cerebral changes much less marked than in the Gambian form, and limited mostly to the leptomeninges, but also that inflammatory changes, particularly

of the serous membranes and heart, form an important feature of the disease (cf. Gambian sleeping sickness).

Immunity.—Although spontaneous recovery has been reported in a few cases, this form of the disease is more virulent than the Gambian, which indicates an even more imperfectly developed mechanism of defense against *T. rhodesiense*.

American Trypanosomiasis (Chagas' Disease)

Etiology.—*Trypanosoma cruzi* is dimorphic in human blood, occurring in a narrow form and in a broad, shorter one. It differs morphologically from the African trypanosomes of man mainly in its length of not over 20 microns, its large parabasal body, and its frequent assumption of a C shape in stained films. Furthermore, it does not usually divide in the blood; multiplication is by successive binary fissions within neuroglial, reticulo-endothelial, and fat cells, and in skeletal, cardiac, and smooth muscle fibers, after reversion to the leishmanial form.

Epidemiology and Transmission.—Most of the cases have been reported from Brazil, Argentina, and Uruguay, but the disease is also known to occur in Chile, Bolivia, Peru, Venezuela, Colombia, Panama, El Salvador, Guatemala, and Mexico. Infected bugs have been found in Paraguay and the United States (California, Arizona, New Mexico, and Texas), and an infected marsupial in Honduras, but in none of these countries have human cases been reported. The geographic distribution may be even wider, for Malamos (1935) found *T. cruzi* in the blood of *Cynomolgus* monkeys from Java. Despite the wide dissemination of the parasite in insect vectors and animal reservoirs, the number of known cases is small. Thus, Talice⁵⁶ gives a total of only 755 confirmed cases of the acute form of the disease up to the year 1940. It is certain, however, that many cases pass unrecognized because of their mildness and their occurrence in backward rural districts.

The main vector is the reduviid or cone-nosed bug, *Panstrongylus megistus* (*Triatoma megista*). Cyclic development and multiplication take place in the intestine, and the infective metacyclic trypanosomes begin to pass to the rectum eight to ten days after the triatome becomes infected by biting man or an animal. Armadillos are the commonest reservoir in South America, but other animals undoubtedly also act in this capacity: cats, dogs, monkeys, bats, the opossum, and wood rats. The last two and the armadillo are the reservoirs in the United States, where *Triatoma protracta* is the vector among animals.

Since the triatome bug defecates at the time of biting, it has been held that the infection is usually acquired by the rubbing of the feces into the tiny skin puncture or into previous abrasions by scratching. Although this does occur, it now seems that in many cases the trypanosomes penetrate through the mucous membranes, particularly the conjunctiva, when the victim rubs the eyes with fingers soiled with the bug's feces. Transmission by the infected

Fig. 260.



Fig. 261.

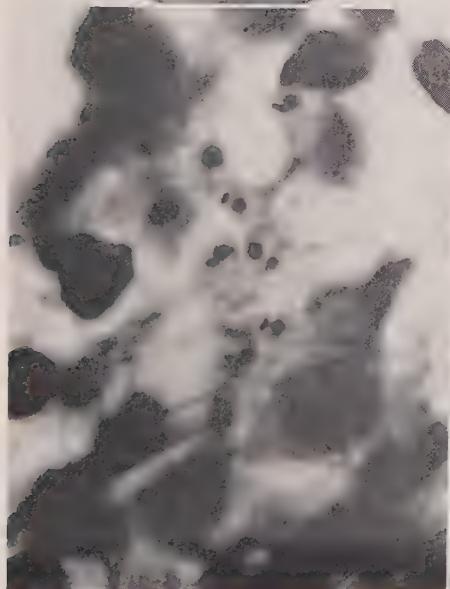
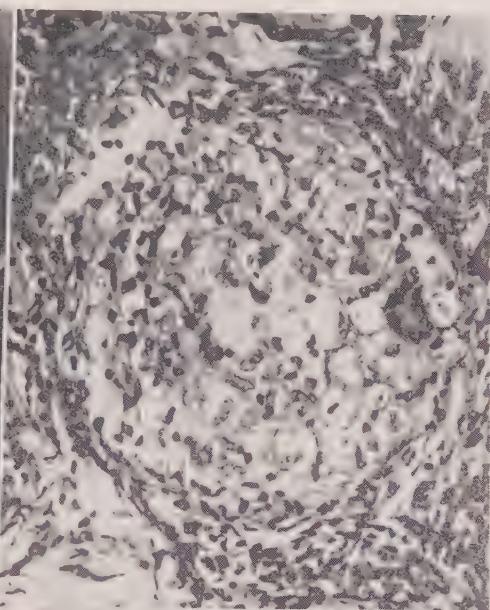


Fig. 262.

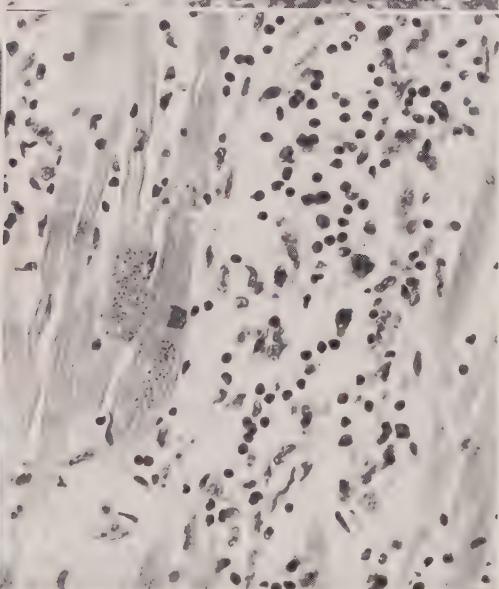


Fig. 263.

Fig. 260.—Romaña's sign in child with Chagas' disease; ophthalmoganglionary chagoma on left side, sixteen days after bug bite. (Courtesy of the late Prof. Mazza, and the Misión de Estudios de Patología Regional del Norte, Argentina.)

Fig. 261.—Chagas' disease. Initial lesion (chagoma) in arm. Focal histiocytic proliferation with formation of giant cells and peripheral infiltration with lymphocytes. (Courtesy of the late Professor Mazza, M.E.P.R.N., Publication No. 46.)

Fig. 262.—Chagas' disease. *Leishmania* in initial lesion (chagoma). (Courtesy of the late Professor Mazza and the M.E.P.R.N., Publication No. 46.)

Fig. 263.—Acute Chagas' disease. Interstitial myocarditis, with loss of muscle fibers and dense infiltration with round cells and eosinophiles; colonies of *Leishmania* in two myocardial fibers at left of center. ($\times 360$.)

maternal milk to lactating infants is possible, as well as directly by the triatome's bite, due to regurgitation of trypanosomes in the insect's stomach.³⁷ Chagas' disease is one of poverty, being present almost exclusively in primitive country dwellings where the reduviid bugs abound. These insects hide away in cracks during the daytime, coming out at night to bite, almost painlessly, usually on the face.

Pathogenesis and Pathologic Anatomy.—Chagas' disease is seen in an acute and a chronic form. The acute form usually begins with the overnight appearance of unilateral or bilateral edema of one or both eyelids, extending in a few days to the same side of the face, while the accessory lacrimal gland enlarges, and the preauricular, parotid, and submaxillary lymph nodes become palpable (Fig. 260). The palpebrofacial edema and the accompanying conjunctival congestion or actual conjunctivitis constitute the sign of Romaña.^{54, 55} The infection becomes general after a few days or weeks, this phase being characterized by generalized lymphadenopathy, enlargement of spleen and liver, fever, firm nonpitting edema of the face and limbs, trypanosomes in the blood, and a hematologic picture of lymphocytosis, frequently accompanied with monocytosis. In a few patients, usually nursing infants, the disease is hyperacute, the end supervening in two to four weeks with signs of meningoencephalitis. Trypanosomes may be found in the blood in individuals with few if any signs of the disease,^{32, 33, 52} indicating the existence of asymptomatic carriers. The presence of signs of thyroid insufficiency, such as myxedema, which for many years obscured the clinical picture of the acute form, is now taken to be due to the coexistence of endemic goiter and cretinism with Chagas' disease in certain regions.^{41, 54} The acute form is less frequent in adults and but rarely fatal, yet Lundeberg⁴² has reported death from myocarditis during the acute phase in a 77-year-old man.

This phase may end in one to three months with complete cure, but in some patients trypanosomes continue to appear in the blood for a prolonged period, or may reappear after a time. Some cases lapse insensibly into the chronic form, usually in the course of several years. Chronic Chagas' disease appears mostly in adults and is still imperfectly known; its principal manifestations are those of grave damage to the central nervous system and heart.

ACUTE CHAGAS' DISEASE.—The conjunctival changes in cases of palpebrofacial edema are of two kinds: (a) An acute conjunctivitis characterized by epithelial erosion, dense superficial infiltration with polymorphonuclears, and numerous leishmania beneath the eroded epithelium. (b) A chronic inflammatory process attended by marked edema of the connective tissue, the formation of deep-seated lymphoid nodules and tubercle-like groups of histiocytes, and a subepithelial lymphangitis with perivascular infiltration by plasma cells and lymphocytes. The first is considered a true trypanosomal conjunctivitis marking the portal of entry and, therefore, of exogenous origin, while the second is a cellulitis of endogenous origin and does not represent a conjunctival portal of

entry. The first occurs in 4 per cent and the second in 96 per cent of the cases thus far studied by biopsy of the conjunctiva.⁵¹ Other investigators interpret the conjunctival and palpebral inflammation and edema as indicative of a conjunctival portal of entry in most cases.

When the skin is the portal of entry, the primary lesion consists of a red papule that may resemble a furuncle. The main microscopic alterations are necrosis of the epidermis, infiltration of the epidermis and superficial parts of the derma with polymorphonuclears, formation in the derma of foci of histiocytic proliferation (Fig. 261), and extensive fat necrosis in the subcutaneous fatty tissue. Lymphangitis is a prominent part of the picture, with the formation of inflammatory nodules along lymphatics in the derma. Leishmania are abundant in histiocytes and fat cells (Fig. 262).⁴⁷

A "chagoma"⁴⁷ is a firm, red skin nodule appearing in the course of acute Chagas's disease, characterized histologically by histiocytic reaction and fat necrosis, and containing leishmania. They may be single or multiple and arise (1) as the initial point of cutaneous inoculation by the insect bite, (2) by lymphatic extension or metastasis from the initial skin lesion of entry, and (3) by the distant, hematogenous transport of parasites. The initial lesion represents a nidus of multiplication of the parasites in histiocytes and fat cells, and within the fibers of the nearest muscle. From here they pass to regional lymph nodes and to the blood stream, after changing to the trypanosomal form, to settle in certain organs and tissues, particularly in the heart, skeletal muscle, and brain.

The enlarged accessory lacrimal gland shows dense infiltration of the interstitial tissue with polymorphonuclears and lymphocytes, without frank suppuration, but accompanied by the formation of foci of histiocytic proliferation in which giant cells are found.⁴⁶ In the enlarged regional lymph nodes the histologic picture is characterized by diffuse lymphoid and nodular reticulum cell hyperplasia, accompanied by the formation of giant cells in the latter nodules.⁴⁹

As in African trypanosomiasis, an exanthematos eruption may appear during the acute phase of Chagas' disease. It generally consists of a pink, maculopapular rash on the thorax or elsewhere, and may be circinate or morbilliform. Histologically there is perivasculär infiltration with round cells in the derma and with more numerous polymorphonuclears in the deeper parts of the epidermis and papillary portion of the dermis. The infiltration also extends to the subcutaneous fatty tissue. There is some proliferation of histiocytes, and leishmania have been found in the lesions within macrophages.

External examination after death may reveal generalized subcutaneous edema of the face and extremities, of a firm, elastic, nonpitting type. The cervical, axillary, and inguinal lymph nodes may be enlarged. The peritoneal, pleural, and pericardial cavities usually contain slight to moderate amounts of light green fluid, in which trypanosomes may be demonstrable, and petechial hemorrhages appear in the serous membranes.

The heart is flabby, and it is enlarged because of dilatation of the left ventricle. The myocardium is pink, with pale or light gray streaks and areas. Microscopically it is the seat of an intense, focal, and diffuse myocarditis (Fig. 263). The muscle fibers are widely separated by histiocytic proliferation and infiltration with plasma cells, lymphocytes, and fewer polymorphonuclears. At many points they undergo waxy degeneration, necrosis, and subsequent phagocytosis by macrophages. Leishmania are found here and there, often in large numbers, within the muscle fibers, in rows or in cystlike dilatations. The skeletal musculature in various parts of the body may undergo parasitization, as above, and focal interstitial infiltration of the same kind as in the myocardium.

The brain is normal grossly, or it shows congestion and edema of the leptomeninges, small hemorrhages, and excessive subarachnoid fluid. Microscopically the leptomeninges are lightly and diffusely infiltrated with macrophages and lymphocytes. Small groups of neuroglial and mononuclear cells form in the white matter of the cerebrum, basal ganglia, cerebellum, pons, medulla, and spinal cord, usually at a distance from blood vessels. Leishmania are found within enlarged neuroglial cells, at times in large numbers, but they may be scarce in the more acute cases, in which they localize primarily in the myocardium.

CHRONIC CHAGAS' DISEASE.—There are but few autopsies on record performed on chronic cases of the disease. Cardiac hypertrophy with interstitial fibrosis and focal lymphocytic infiltration of the myocardium have been described.^{44, 45} Chagas³⁴ has found fibrotic changes in various organs, particularly the heart and brain, with the persistence of active inflammatory foci containing leishmania.

Visceral Leishmaniasis (Kala-azar)

Etiology.—The life cycle of *Leishmania donovani* comprises two developmental stages: the aflagellate in man and the flagellate in insects. In Romanowsky-stained smears the leishmania is round or ovoid, and 2 to 5 microns in length by 1 to 2 in breadth. A well-defined cell membrane encloses the light blue cytoplasm. The nucleus is prominent, spherical, pink or dark red, and eccentric. Perpendicular or tangential to it is the bright red or violet, rod-shaped kinetoplast. Under high magnification the latter is seen to be composed of a rodlike parabasal body and a minute dot, the blepharoplast. From the kinetoplast to the cell membrane there extends a delicate red filament, the axoneme (rhizoplast), which is the root of the undeveloped flagellum.

Epidemiology and Transmission.—Kala-azar occurs in eastern India, northern China (sporadic cases in the south), southern Manchuria, Turkestan, Transcaucasia, the Mediterranean littoral and islands, Egypt, Anglo-Egyptian Sudan, Nigeria, French Equatorial Africa, and South America (Brazil, Paraguay, and Argentina). Infantile kala-azar predominates over the adult form in the Mediterranean littoral and islands, and is also found in Portugal and Hungary.

In India, where kala-azar has been studied most intensively, the disease is generally limited to alluvial valleys with high humidity and a temperature that averages 29° C. (85° F.) in the summer and never reaches below 15.5° C. (60° F.) in winter. Its appearance in a locality is usually traceable to the previous introduction of a human case. The infection tends to cling to certain houses, and its distribution is mainly rural, at altitudes of not over 4,000 feet. Though usually sporadic, it may break out in epidemic form. Both sexes are equally affected, but it is rare after 40 years of age.

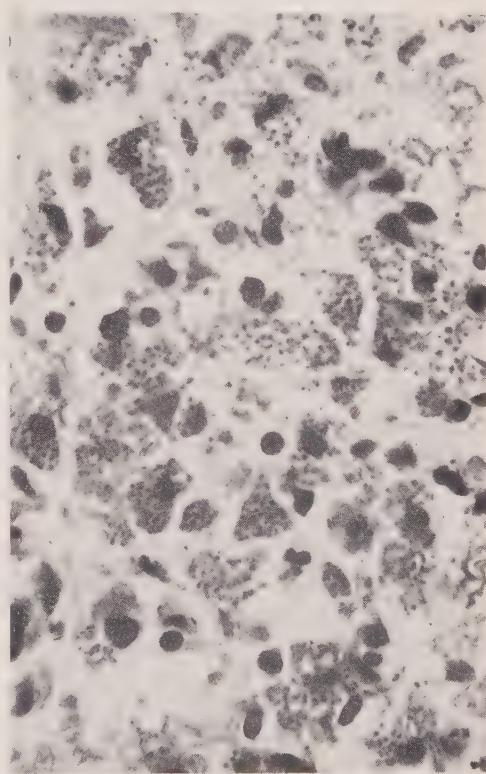


Fig. 264.—Spleen of Indian case of kala-azar. The reticuloendothelial cells of the pulp and sinuses become distended with *Leishmania*. ($\times 776$.)

Transmission is by the bite of *Phlebotomus* sand flies, which are apt to be found under the conditions above mentioned, the species varying in different countries. Final proof of the transmission by *Phlebotomus argentipes*, the vector in India, came in 1942,⁴⁶ after a long series of investigations. Leishmania are ingested with the blood of patients when the sand fly bites. They turn into flagellated forms in the midgut, and these multiply and pass forward to the pharynx and mouth of the insect. It takes seven to nine days for these forms of the parasite to be able to reach the proboscis and so to infect man. It seems that man is the main reservoir of the infection, but the dog has come under suspicion because in some regions,

like the Mediterranean, it is very frequently found infected.

It is possible that transmission may rarely take place by direct contact with patients, for in a certain proportion of cases viable leishmania are present in the secretions of the nose and throat⁶¹ and, infrequently, in the feces and urine. There have been a few cases of probable transplacental transmission from mother to child, which is not an infrequent occurrence among animals experimentally infected in the laboratory.

Pathogenesis and Pathologic Anatomy.—Clinically, kala-azar is characterized by fever and chills, continuously or in periodic accessions, and frequently with two daily rises and remissions, splenomegaly and less marked hepatomegaly, dark pigmentation of parts of the skin, and a marked leukopenia. Death may take place in four months, or, after two to six weeks a state of chronicity with cachexia sets in and life is prolonged for about two years.

Upon entering the body, the infective flagellate reverts to the leishmanial stage and either invades reticulo-endothelial cells or is phagocytosed by them. Within them the parasite multiplies enormously and is transported to various parts of the body. The organs and tissues with a greater abundance of reticulo-endothelial elements bear the brunt of the disease: the spleen, liver, and bone marrow. Lymph nodes are involved to a variable extent.

At autopsy, great emaciation and a marked pallor of the skin and mucosae are usually encountered. The abdomen is protuberant. Lighter-skinned individuals frequently present considerable darkening over the dorsum of the hands, feet, and abdomen (kala-azar means the "black disease").

The spleen is enlarged and moderately firm. In exceptional cases it has weighed 4,000 grams in an adult and 1,000 grams in a child, but the average is approximately one-half the above weights, or less, depending on age and duration of the illness. Perisplenic adhesions and infarcts are frequently observed. The pulp is dark red, with ill-defined lymphoid follicles and trabeculae. Microscopically there is marked congestion, and a remarkable proliferation and enlargement of the reticulum cells of the red and white pulp, many of which undergo mobilization as macrophages (Fig. 264). Their cytoplasm is clear and contains few or numerous leishmania (Leishman-Donovan bodies). In sections stained with hematoxylin and eosin the organisms appear as rounded or oval bodies shrunken to about 2 by 3 microns. The nucleus is prominent, dark blue, and frequently hides the kinetoplast. Plasma cells are found in the pulp, and are said to be particularly numerous when the parasites have disappeared under treatment and the histiocytic response has become less prominent.⁶² Chronic cases show some fibrosis of the pulp. The malpighian corpuscles may be normal, or else show hypertrophy and proliferation of reticulum cells in the center, as well as central hyaline degeneration. In children, neutrophilic myelocytes occur in the pulp.

The liver usually weighs over 2,000 grams. The capsule is tense, and the parenchyma is pale

yellow from fatty change, or congested and red. Microscopically, the Kupffer cells are greatly swollen, narrowing the congested sinusoids; they may contain leishmania and hemosiderin pigment. The liver cells undergo fatty degeneration peripherally and are often atrophied. In heavily parasitized cases there are occasional leishmania in them. The portal spaces are lightly infiltrated with lymphocytes and macrophages, the latter at times engulfing leishmania. In some livers hepatic edema is in evidence, probably as a result of cachexia, and then the delicate membrane lining the cords of liver cells is separated from them by coagulated protein.

The bone marrow of the diaphysis of the long bones, fatty in the normal adult, becomes red and hyperplastic. Promyelocytes are more numerous than the maturer forms. The reticulum cells and those lining the sinuses enlarge and proliferate, and leishmania may be found in them. The myeloid and reticulo-endothelial cells predominate over the erythrocytic. Among the latter there is a notable diminution in the number of normoblasts. There are small groups of lymphocytes, while plasma cells may be numerous, particularly in very active infections.⁶²

The lymph nodes in various locations, particularly the mesenteric and femoral groups, are slightly to moderately enlarged, soft, and either pale or congested. Microscopically, the main change is an increase in the number of macrophages, developing from the littoral cells of the sinuses and from the reticulum cells. These cells may contain leishmania in cases in which the other organs are free. The lymphoid tissue is infiltrated with plasma cells in heavy infections.

Intestinal involvement is frequent, especially toward the end in fatal cases. This may be in the form of large, dark red, and elevated ulcers of the colon that extend to the submucosa or muscle coat. Microscopically they are not characteristic, but parasitized macrophages may be found in their base. In other cases there is a terminal, nonspecific, ulcerative colitis, or a complicating dysentery of amebic or bacillary origin. In active infections the endothelial cells of the lymphatic capillaries in the tunica propria of the jejunum and other parts of the intestine enlarge and proliferate, and are filled with leishmania. In the small intestine this renders the villi large and bulbous.⁶⁶

Ocular involvement is manifested in various ways. The more common, encountered in about one-third of Chinese cases,⁶⁸ are multiple hemorrhages into the retina.

In some cases there has been found extra-medullary hematopoietic tissue forming a soft, velvety, bright red, thin layer between the vault of the skull and the dura mater.⁶² Capillary damage, although not demonstrable histologically, is evidenced in the common and important sign of bleeding from the nose and gums.

Not infrequently, enlarged, parasitized histiocytes are found on microscopic examination in other organs: alveolar septa and peribronchial connective tissue of the lung, glomerular capillaries of the kidney, cells lining the suprarenal sinusoids, interstitial connective tissue of the pancreas and testis, in tonsils and derma,

and in other organs. In all these locations, infiltration with lymphocytes and plasma cells may take place. In the blood stream leishmania may be present in large mononuclear cells and, more rarely, in neutrophiles.

Dermal involvement in kala-azar is of two main types: one that occurs toward the end of the treatment, or one or two weeks thereafter, and another that comes on one or two years after treatment, or several years after spontaneous cure. The first is frequent in the Sudan,⁶⁴ and the second, known as dermal leishmanoid or post-kala-azar dermal leishmaniasis, in India.⁵⁹ In the former there may occur all gradations from an inconspicuous punctate eruption to papular, nodular, and verrucous lesions, at times in the same patient. They are mostly in the face and neck, but may be generalized. They do not ulcerate, and produce neither pain nor itching.⁶⁴

In post-kala-azar dermal leishmaniasis there appear minute points of depigmentation that grow to patches reaching about 0.8 cm. in diameter, and are usually general in distribution. Approximately one year later, soft, pinkish-yellow nodules the size of a split pea develop in the areas previously affected, and may bear a strong resemblance to leprosy, particularly when there is erythema. The last stage is very rare, and consists of the formation, after ten to thirty years, of xanthoma-like, orange-colored plaques, of either local or general distribution. Histologically, in the depigmented plaques the epidermis is normal, except for diminution of pigment. The subpapillary zone of the derma is edematous and its blood vessels dilated, while just below this there is slight infiltration by histiocytes. The elastic fibers are fragmented. No parasites may be visible in these lesions, but cultures in the Nicolle-Novy-MacNeal (N. N. N.) medium may be positive. In the second stage there is atrophy of the epidermis, depigmentation, and obliteration of dermal papillae. Dermal changes are as in the preceding lesion, except for fibrosis in the mid-dermal zone of infiltration with histiocytes, and for the presence of parasitized multinucleated cells. The orange-colored plaques are very similar to the preceding, but there is still greater fibrosis and congestion, and parasites are abundant.⁵⁹

Complications.—The gravest complication is noma, usually appearing in the terminal stage of kala-azar among infants, children, and young adults; it is rarely seen in adults. Pneumonia and ulcerative colitis (nonspecific, amebic, or bacillary) are other common and important complications. In a few cases agranulocytosis supervenes among the debilitated under treatment, and is usually fatal.

Pathologic Physiology.—While the disease is active, the serum albumin is reduced from the normal of 4.6-6.7 per cent, to 2.8 or 3, and the globulin rises from 1.2-3.3 per cent, to 4. The change in the globulins results principally from a marked increase in the euglobulin content. The clinical diagnostic tests of coagulation or jellification of kala-azar serum by formaldehyde, antimony, and other substances, and the flocculating effect of distilled water, are based on these alterations.⁶⁰ Similar changes occur

in leprosy, tuberculosis, malaria, trypanosomiasis, cirrhosis of the liver, cancer, and syphilis. The white blood count in the well-established case is usually below 4,000 and may be as low as 600. There is anemia of secondary type.

Immunity.—No individual or race is naturally immune to *L. donovani*. However, spontaneous cures of kala-azar without specific treatment are known to occur. The mortality in adults is roughly 90 per cent among the diagnosed cases, yet it is most probable that slight, undiagnosed cases are much more frequent than is generally believed. In infantile kala-azar the mortality among the untreated is about 80 per cent.

The complement fixation test that utilizes the Witebsky-Klingenstein-Kuhn fraction of the human tubercle bacillus as antigen appears to be highly specific and efficient in diagnosis.⁶⁷

Mucocutaneous or American Leishmaniasis (Espundia)

Etiology.—*Leishmania brasiliensis* does not differ morphologically, or in its behavior in experimentally infected animals, from *L. tropica*. Still, serologic studies by means of agglutination and complement fixation reactions^{75, 81} and its mode of growth in solid media⁸⁰ and the hen's egg,⁷⁴ suggest that *L. tropica*, *L. donovani*, and *L. brasiliensis* are not identical. Furthermore, only a few cases of oronasal leishmaniasis have been seen complicating oriental sore in Italy and the Sudan.

Epidemiology and Transmission.—The disease is present in Central America (Yucatán, Guatemala, Honduras, Costa Rica, and Panama), and in all countries of South America with the exception of Chile. It occurs mostly in the dense and humid forests during the rainy season, especially attacking forest workers and collectors of chicle gum and rubber. No race, age, or sex is exempt, but because of the conditions under which the disease is acquired, men are more frequently its victims, and it represents a serious occupational hazard. Like oriental sore, it is directly inoculable, but the cutaneous lesions are most frequently acquired by the bite of sandflies or some other hematophagous insect.

The reservoir, insect vector, and principal mode of transmission have not yet been fully demonstrated for this disease. However, *Phlebotomus* sandflies, particularly *P. intermedius*, have been found in all the foci so far investigated.

Pathogenesis and Pathologic Anatomy.—The disease is indistinguishable from oriental sore when the lesions are exclusively cutaneous. In American leishmaniasis, however, constitutional symptoms are present in some cases while the lesions are still cutaneous. In about 20 per cent of cases the oronasal membrane is involved. The cutaneous ulcers frequently develop in the ear margins, and the lesions are less responsive to treatment with pentavalent compounds of antimony, with the result that death often results from pneumonia, septicemia, or cachexia.

In advanced cases of mucosal involvement there is secondary anemia and marked wasting.

The dermal lesions appear mostly in exposed parts. The incubation period has not been definitely determined, but is probably two to three months. The clinical and histologic appearance and the evolution of the cutaneous lesions are as in oriental sore, except for the previously mentioned involvement of the external ears among forest workers.

From a few months to fifteen years after healing of the dermal lesions, in a certain number of cases, the mucous membrane of the upper respiratory and alimentary passages becomes involved in a chronic inflammatory process caused by *L. braziliensis*. This begins in the anterior third of the nasal septum and may spread in the course of years to all of the nasal cavity; more rarely, the soft and hard palate, the buccal mucosa, tongue, pharynx, and even the larynx may be involved. The disease, however, is predominantly nasal. The lesions may be mainly infiltrative, papillomatous, or ulcerative. The mucous membrane swells and reddens; later there appear pink nodules and vegetations that bleed easily to the touch. Yellow or dark red crusts form, producing nasal obstruction, and the secretion irritates the upper lip, which swells and may ulcerate. After a time the cartilaginous septum is destroyed, and the nose becomes depressed, while the overlying skin is swollen and reddened. The air sinuses are but rarely involved.

Microscopic study of the earliest, nonulcerated lesions obtainable shows the changes beginning deep in the mucous lining of the nasal septum, with focal infiltrations of lymphocytes and plasma cells, and lesser numbers of polymorphonuclears and macrophages in the adventitial tissue of arterioles. Rare leishmania are seen in the macrophages. At a later stage the infiltration becomes diffuse, more dense, and is accompanied by marked congestion and edema. Plasma cells predominate over lymphocytes and fibroblasts begin to proliferate. There is enlargement and proliferation of histiocytes, isolated and in plaques, as well as occasional formation of giant cells. The histiocytes frequently contain one or more leishmania. The endothelial cells of some of the capillaries are swollen. Erosion of the surface epithelium occurs in places, and polymorphonuclears will be found in the superficial parts of the lesion only. In the later course of the lesion the surface epithelium thins out and disappears, with the formation of very shallow ulcers. The inflammatory changes in the propria again become predominantly focal in character, there being groups of histiocytes and occasional giant cells, surrounded by lymphocytes and plasma cells. A few leishmania will be found in the center of the cell aggregates. Some of the nodules will undergo necrosis, while others are replaced by fibroblasts that grow in from the periphery.

The leishmania probably reach the mucous membrane by way of the blood stream from dormant cutaneous foci, since it is difficult to conceive of the oronasal lesions as arising from the bite of an insect, or by contact with another case, and autoinoculation is impossible in the numerous cases in which they develop after healing of the cutaneous lesions.

Immunity.—The cutaneous sores heal permanently. That a true immunity does not result in a proportion of the cases is shown by the development of mucocutaneous leishmaniasis. The latter shows but little tendency to spontaneous regression.

Cutaneous Leishmaniasis (Oriental Sore)

Etiology.—*Leishmania tropica*, the cause of oriental sore, does not differ morphologically, in human or animal tissues, in insects or in cultures, from *L. donovani*. In human and animal tissues it occurs in the form of leishmania, and in insects and cultures as leptomonads. The parasite is strictly cutaneous in localization in man, in contradistinction to the generalized distribution of *L. donovani* in kala-azar. In mice, inoculation into the skin may result in a local lesion, while intraperitoneally a granulomatous and fibrotic lesion about the testes often develops prior to visceral involvement.⁸⁹

Epidemiology and Transmission.—Oriental sore is found in the Mediterranean islands and littoral, in the Near East (Palestine, Syria, Armenia, Iraq, Persia, Arabia), Transcaucasia, Turkestan, northwestern India, Egypt, Abyssinia, the Anglo-Egyptian Sudan, Nigeria, French Equatorial Africa, and Angola.

In 1921 the Sergeant brothers, and Parrot, Donatien, and Béguet⁹⁰ produced oriental sore in man by inoculating the scarified skin with an emulsion of crushed sand flies (*Phlebotomus papatasii*). Transmission by the bite of the sand fly under experimental conditions was difficult and uncertain until Adler and Bers⁹² reproduced the disease in a majority of volunteers, by modifying the manner in which the sand flies were kept and infected in the laboratory. It is easily transmissible by direct contact, and self-inoculation by means of scratching is frequent.

Man and dogs are the main reservoirs of the infection in most parts. In Turkestan, however, Penjdeh sore, which is a local variety of cutaneous leishmaniasis, has wild rodents (gerbils, marmots) for a reservoir.⁸⁸

Pathogenesis and Pathologic Anatomy.—Oriental sore may be single or multiple. A small red papule first appears, usually in parts of the body which are exposed at night-time to the bite of sand flies. It soon develops thin, white or brownish scales. As it grows it becomes violet and more scaly, and a red and indurated zone develops about it. After three weeks to four months an ulcer forms which when fully developed has sharply defined, elevated, and undermined borders (Fig. 265). The ulcer then averages 2.5 to 3 cm. in diameter but may be much larger. The base is usually covered by a crust, and there is a thin, pale, and scanty secretion. Smaller ulcers at times develop about the main one and may later merge together, or there appear small subcutaneous nodules in its vicinity. Verrucose and lupoid lesions are sometimes seen. Healing begins from two months to a year or more after onset, and is usually slow and unsteady. A depressed scar always remains, and in many cases is disfiguring.



Fig. 265.—Oriental sore. Two well-developed sores of lower leg. The excavated center and swollen borders are well shown. (AFIP No. 1440-1.)

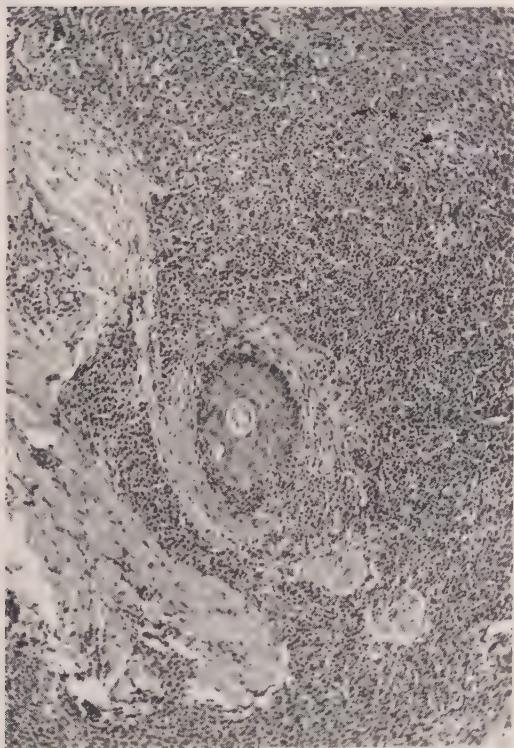


Fig. 266.—Oriental sore. Infiltration of derma with lymphocytes and plasma cells becomes almost massive at height of development of oriental sore. ($\times 80$)

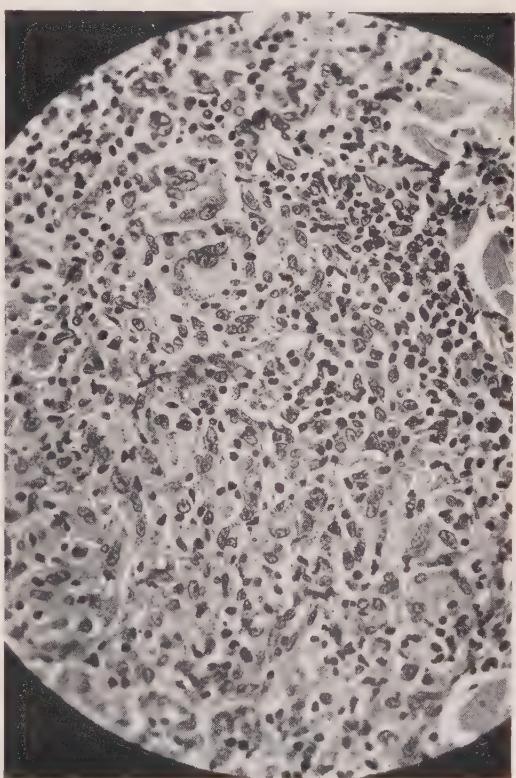


Fig. 267.—Oriental sore. Zones of histiocytic proliferation and giant cell formation may appear among the lymphocytes and plasma cells in the derma. *Leishmania* are just visible at this magnification in some of the histiocytes and giant cells. ($\times 180$)

Microscopically there are multiple, large, and dense foci of infiltration about blood vessels and skin appendages, mostly with plasma cells, but also with lymphocytes and an occasional eosinophile (Fig. 266). Here and there, isolated and in groups, there are swollen histiocytes which often contain leishmania. In the foci of histiocytic proliferation occasional giant cells are seen (Fig. 267). The endothelial cells of capillaries are swollen. The infiltration extends through the thickness of the derma, separating the collagenous bundles from one another, and into the subcutaneous fatty tissue. Toward the periphery of the lesion the infiltration is lighter and more focal. Healing begins with a peripheral fibrosis, that gradually extends centrally. The epidermis first becomes hyperkeratotic and acanthotic, and the rete pegs are much elongated. As the nodule grows, the epidermis becomes thinner and undergoes necrosis when ulceration occurs.

The subcutaneous nodules that sometimes develop in the neighborhood of the sores resemble the primary dermal lesion histologically, but are attended by more fibrosis, and appear to develop in connection with lymphatics. They represent localized inflammatory foci about leishmania escaping from the main dermal lesion along lymphatics.⁸⁶

Immunity.—Oriental sore confers a solid and lasting immunity.

Malaria

Etiology and Life Cycle.—The malarial protozoa belong to the genus *Plasmodium*, of which there are four species naturally infective to man: *P. vivax* (of tertian malaria), *P. malariae* (of quartan malaria), *P. falciparum* (of pernicious, malignant, or estivautumnal malaria), and *P. ovale* (of ovale malaria). They pass through an endogenous or asexual cycle in man, multiplying by fission (schizogony), and an exogenous cycle in the mosquito, in which they multiply sexually (by sporogony).

The cycle in man begins with the introduction of the sporozoites by the mosquito. It has recently (1948) been demonstrated that there follows an exo-erythrocytic phase occurring in the liver, probably within hepatic cells. After an incubation period of about 7 to 10 days, the parasite passes into the blood stream to enter red blood cells.^{92a} The parasite grows and multiplies within the latter, passing through the successive developmental stages of trophozoite, schizont, and merozoite. In Romanowsky-stained films the cytoplasm of all forms stains blue and the nuclear chromatin bright red. The trophozoite is a delicate blue ring of cytoplasm with one or two red chromatin dots. It increases in size, the cytoplasm assumes a very irregular contour, and the chromatin is visible as one or more dots, threads, or irregular masses, while a few brown granules of pigment appear. The schizont develops by condensation of the cytoplasm into an oval or round mass that grows until it fills the red blood cell, then segmenting into a number of merozoites. These are oval or spherical bodies with blue cytoplasm and a red or purple, eccentric nucleus. They are set free in the circulation by rupture of the eryth-

rocyte; while some are lost to the defense mechanism of the host, others invade red blood cells and repeat the cycle. The schizogonous cycle lasts forty-eight hours in the case of *P. vivax* and *P. ovale*, seventy-two hours for *P. malariae*, and thirty-six to forty-eight hours for *P. falciparum*. There are morphologic differences between the various forms of the malarial parasites that allow the experienced observer to distinguish the species by microscopic examination of the blood.

The exogenous cycle in the mosquito takes place as follows: Some of the merozoites grow as solid, round or crescentic parasites representing male and female forms known as *microgametocytes* and *macrogametocytes*, respectively. Taken up by the appropriate mosquito on biting a patient or carrier, the microgametocyte reaches the stomach and throws out delicate filaments, each one containing chromatin material, and becoming liberated as a *microgamete*. After extrusion of a polar body the macrogametocyte becomes the *macrogamete*, into which the microgamete then penetrates. The fertilized cell is the zygote, which elongates and mobilizes to form the oökinete. This moves into the wall of the stomach, beneath the external limiting membrane; as it enlarges into an oöcyst, numerous, minute, spindle-shaped *sporozoites* develop within it. The oöcyst ruptures into the body cavity, from which the sporozoites invade all parts of the mosquito's body. Those that reach the salivary glands pass down the proboscis when the insect bites, and so infect man.

The cycle in the mosquito requires seven to twelve days for completion, and can take place only in members of the genus *Anopheles*. Very numerous species of anophelines are capable of transmission, but the principal vector in the United States is *A. quadrimaculatus*, in the Caribbean *A. albimanus*, and in Europe *A. maculipennis*. *A. gambiae* is the most dangerous vector. It breeds prolifically in small, shallow collections of water, very close to dwellings of man, on whom it prefers to feed, and is capable of developing very high rates of salivary gland infection. It is, therefore, apt to provoke explosive outbreaks attended by a high rate of incidence and a high mortality, even in the case of vivax malaria. Africa is its habitat, but with the newer, faster methods of transportation, the danger is always present of its spread, as happened in 1930, when it appeared in Brazil, giving rise to severe epidemics.

Epidemiology.—The more dangerous *falciparum* malaria occurs mostly in tropical and subtropical regions, while *vivax* infections extend as far as southern Sweden and southern Argentina. Quartan malaria, for unknown reasons, is very irregularly distributed in the tropics and subtropics, and is relatively rare; it is more common in temperate regions than in the tropics. Ovale malaria is the rarest of all. It is found mainly in Western and Central Africa. Malaria is the most important infectious disease of man, both as a morbidity and a mortality factor. In 1932 the League of Nations estimated over three hundred million yearly cases throughout the world.

The main epidemiologic factors at play in the propagation of the disease are the presence

(1) of anopheline mosquitoes of certain species, and (2) of active or latent human cases from which the former can become infected, in (3) regions where climatic and hydrographic conditions are favorable to the multiplication of the insect vector, and to completion of the sporogonous cycle of the parasite. A low altitude, a warm moist climate with abundant rainfall, the presence of pools of water from partial drying of streams, or the presence of marshes, and the artificial collecting or impounding of waters under certain conditions are ideal for the breeding of the vector, and thus favor a high endemic rate or the occurrence of epidemic outbreaks. These outbreaks are to be expected when nonimmunes, like bodies of troops, or shifting masses of people, move into malarious areas in which the above conditions prevail. In endemic regions the disease is contracted in childhood, and a tolerance or immunity is developed as the individual grows. Active infections are, therefore, more frequent among children than adults.

Congenital infection is possible but rare. It is taken to result from placental tears that allow infected maternal blood to mingle with the fetal, or by schizonts in the mother's blood entering through skin abrasions at childbirth. Blood transfusions will transmit malaria when the donor's blood contains schizonts, but gametocytes alone are not infectious, and they do not multiply in the human host. A highly malignant form of falciparum malaria has been transmitted among drug addicts by the common use of unsterile syringe and needle.

Pathogenesis and Pathologic Anatomy.—In vivax, quartan, and ovale malaria the clinical picture is marked, in fully developed and typical acute cases, by periodic paroxysms consisting of a shaking chill followed by high fever and ending in drenching perspiration as the temperature falls. The paroxysms last four to ten hours, and recur every third day in vivax and ovale infections and every fourth day in quartan. For a number of days, at the beginning of vivax malaria, the maturation of the parasites is not wholly synchronized, merozoites being released daily by different groups of parasites, and thus the febrile attacks show a daily periodicity during that time. In falciparum malaria the onset is often insidious, the rigors are rarely as strong as in the other malarias, the paroxysms are less regular, and in heavy infections the fever is apt to be continuous. Frequently, in all forms of malaria, the typical paroxysm is greatly modified, both in character and regularity.

P. vivax, *P. malariae*, and *P. ovale* only rarely produce death directly and are, therefore, referred to as benign malaria. Even in the untreated, the rule in these infections is for the symptoms to disappear in a number of months, after one or more relapses, with cure supervening after a more or less prolonged period of latency. It is not known where, and in what form, the parasite may sojourn during latency; an exo-erythrocytic phase in reticuloendothelial cells, perhaps in the spleen and bone marrow, has been suggested.

ACUTE BENIGN MALARIA.—Our knowledge of the pathology of these forms is based mostly

on accidental deaths in the course of natural and therapeutic malaria. The pathologic alterations are mainly those of secondary anemia and of reticulo-endothelial response to the malarial parasite and pigment. The organs and tissues primarily affected are the spleen, liver, and bone marrow. The spleen is large, with a soft pulp to which the malarial pigment imparts a chocolate color or a gray cast, depending on the duration and heaviness of the infection; in early cases the color is normal. The lymphoid follicles may be prominent or inconspicuous. Microscopically, the reticulum cells of the red pulp and littoral cells of the sinuses are enlarged, and there are numerous macrophages in the cords of Billroth. The germinal centers are large, and present prominent reticulum cells and young lymphocytes, while the number of adult lymphocytes becomes depleted. The malarial pigment is most abundant in the reticular cells and macrophages of the red pulp. In earlier infections it is brown, nonrefractile, and finely divided; later it forms dark clumps. In addition to pigment the macrophages ingest malarial parasites, red blood cells, occasional leukocytes, and cell debris. The parasites are easier to detect in smears of the pulp than in Giemsa-stained sections.

The liver is large and congested, and may present a gray cast. There may be noted a fine yellow mottling from fatty change. Congestion of the sinusoids and increased phagocytic activity of the Kupffer cells are the more prominent microscopic features. The latter are large; their cytoplasm contains the same elements as the splenic macrophages. The hepatic tissue may undergo cloudy swelling or fatty change, and a few lymphocytes may infiltrate the portal spaces.

The bone marrow is red or brown. It shows increased activity of both the myeloid and the erythroid series. The erythroid hyperplasia is mostly normoblastic, but megaloblasts are said to be present in many cases.⁹⁴ Despite the increased activity of the granulocytic series, the number of leukocytes in the peripheral blood is either normal or diminished. There is enlargement of reticulum cells and mobilization of macrophages, both of which behave as in the spleen.

A fulminating type of vivax malaria has been described in youths of 4 to 17 years. The onset is very sudden, and death occurs in two or three hours. Parasites are very scanty in the cerebral capillaries.¹⁰⁸

PERNICIOUS MALARIA.—Wasting and anemia are more apt to develop in this form of malaria. Although the general tendency is toward a cure, there is always the danger that grave manifestations may arise, such as bilious remittent fever and the pernicious attacks. The former is characterized by accessions of fever, icterus, and gastric distress with vomiting. Its gravity resides in its tendency to chronicity, with the development of anemia and cachexia. The pernicious attacks are dreaded for their sudden onset and high mortality. Their manifestations are most protean. Cerebral malaria, the commonest, may be preceded by low or very high fever, and begins slowly or with unexpected suddenness; convulsions and coma mark

the fully developed syndrome. The algid forms come next in frequency, and are characterized by evidences of shock, such as great prostration, a cold and clammy skin, and a low blood pressure. The algid may assume gastric, choleraic, dysenteric, and hemorrhagic forms. Despite the fact that the presenting symptoms may point to predominant involvement of one organ or system, a strict clinicopathologic correlation is often impossible at autopsy.

The greater gravity of malignant malaria is due mainly to the following: *P. falciparum* multiplies to a much greater extent than the benign species; it leads to more frequent relapses, has a great tendency to chronicity, and it concentrates in large numbers in visceral capillaries. *P. vivax* invades young erythrocytes, while *P. malariae* prefers the older ones. *P. falciparum*, on the other hand, has no such limitations to its multiplication, for it may parasitize red blood cells of all ages.

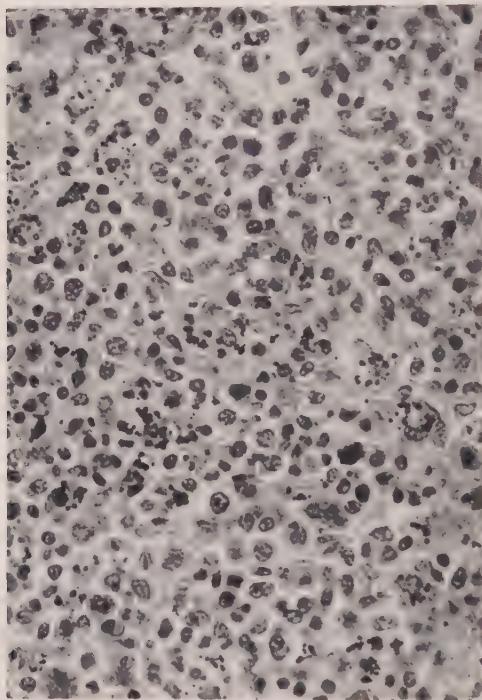


Fig. 268.

Fig. 268.—Spleen in acute falciparum malaria. Marked reticuloendothelial hyperplasia and loss of outline of sinuses; finely divided malarial pigment within red blood cells and phagocytes. ($\times 360$.)

Fig. 269.—Liver in acute falciparum malaria. Cloudy swelling and some disarrangement of hepatic cords; swelling of Kupffer cells, which become laden with malarial pigment and cellular debris. ($\times 360$.)

At autopsy, an icteric tint or sallowness of the skin, and wasting, are frequently observed. In the rare purpuric cases there are numerous and extensive hemorrhages into the skin and serous membranes. In chronic cases there may be subcutaneous edema of the feet and legs, and effusion of clear fluid into the abdominal and pleural cavities.

The spleen is enlarged to an average weight of 500 to 600 grams. On section the pulp is extremely soft, and may be diffused. The lymphoid follicles and trabeculae are inconspicuous. The degree of malarial pigmentation varies with the duration of the disease, the pulp being chocolate-colored to gray or almost black. Microscopically there are larger numbers of parasites, and a greater abundance of pigment, than in benign malaria. The pulp is congested and hemorrhagic, so that the limits between the red pulp and sinuses are ill-defined; it may present foci of necrosis. The reticuloendothelial cells are prominent, and engulf malarial pigment and cell debris (Fig. 268). The germinal centers of the follicles are hyperplastic, yet there is marked depletion of adult lymphocytes. Thrombosis of blood vessels and infarct formation supervene occasionally. Frequently, the subintima of trabecular veins is densely infiltrated with lymphocytes and macrophages. The liver also enlarges, often to 2,000

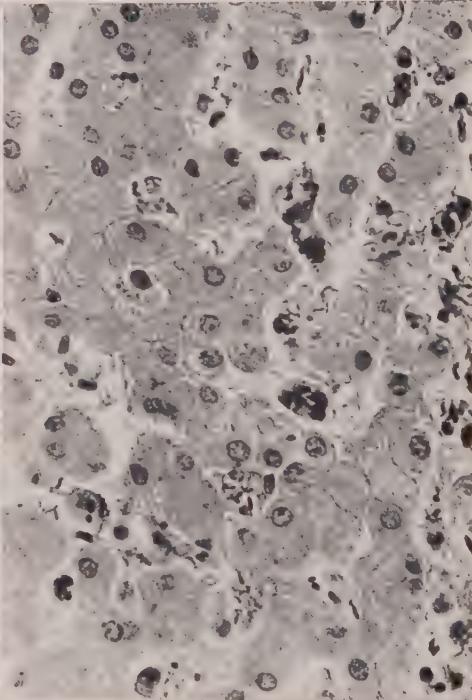


Fig. 269.

grams. Pigmentation is never as marked in this organ as in the spleen. In most cases the hepatic tissue is congested, with a gray cast; in cachetic individuals, a more or less marked yellow mottling may be in evidence from fatty change. Microscopically the Kupffer cells are large and actively phagocytic toward parasites, red blood cells, and malarial pigment (Fig. 269).

The hepatic cells undergo cloudy swelling and some fatty change. Not infrequently, hyaline necrosis takes place in the center of the lobules, and at times the regular arrangement of the hepatic cords is distorted. Pale yellow hemosiderin pigment appears within Kupffer cells, and, less frequently, in the liver cells. The portal spaces contain increased numbers of lymphocytes; in older infections they may show some fibrosis.

The bone marrow undergoes marked myeloid and erythroid hyperplasia. The reticulum cells enlarge, become actively phagocytic, and mobilize as macrophages. Megaloblasts are found in small numbers in most cases. Pigment and parasites occur as in the spleen. In the *suprarenal glands* the cortical lipoids become depleted, and the cells of the fasciculate zone have a shrunken appearance. There may be hemorrhage, limited or extensive, and thrombosis may supervene. Some of these alterations may be significant, for in malignant malaria there may be bronzing of the skin, extreme adynamia, and other features suggestive of impaired suprarenal function. The kidneys are slightly enlarged and congested. Engorgement of blood vessels and cloudy swelling, or some fatty degeneration, of the epithelium of the convoluted tubules, are the usual microscopic findings. Some albuminous precipitate is seen in the lumen of tubules and, at times, in the capsular space of the glomeruli.

In pernicious attacks there are enormous numbers of parasitized and pigmented red blood cells in the capillaries and small blood vessels of certain organs. This occurs more frequently in the spleen, liver, bone marrow, brain, and lungs, and less frequently in the kidneys, small intestine, pancreas, heart, and testes. In sections the parasite is oval-shaped and blue, with the pigment in finely divided form or as a large brown clump; it is found within erythrocytes and large mononuclear cells in the blood vessels of most organs and tissues. The latter cells are derived from reticulo-endothelial elements lining splenic, hepatic, and bone-marrow sinuses and sinusoids, and may contain fine granules of malarial pigment in their cytoplasm. Since formalin produces a very confusing brown pigment in tissues by its action on hemoglobin, it should not be used as a fixative in malarious countries.

The brain, in cerebral malaria, may be normal externally and on section, or only congested. It may have a gray cast or a distinct leaden coloration. Petechial hemorrhages are a frequent finding, and may be extremely numerous, externally and on section, particularly in the white matter. The main microscopic alterations are the concentration of parasitized red blood cells in capillaries and the presence of focal hemorrhages, foci of necrosis, and malarial granulomas (glial or Dürck's nodules). The capillaries of the leptomeninges, brain (Fig. 270), cerebellum, and spinal cord are very prominent and filled with parasitized erythrocytes. Although the red blood cells give the impression of being clumped, actual thrombosis is rare. The endothelial cells of these capillaries, although swollen, are not phagocytic for parasites or pigment. The perivascular lymph spaces are dilated and empty, except for rare and slight accumulation of lymphocytes and a few plasma cells. Minute capillary hemor-

rhages are most frequently seen in the subcortical zone of the brain, while in the cerebellum (Fig. 271) they are equally profuse in the various layers; a capillary is usually visible at the center or to one side of the hemorrhage. Minute foci of rarefaction of the cerebral substance, and of demyelination, appear here and there, at times with hemorrhage. In some cases malarial granulomas or glial nodules are found in the white matter. At the beginning these consist of a central capillary, containing clumped and parasitized erythrocytes, surrounded by a small, pink zone of necrosis about which there are extravasated red blood cells and proliferating neuroglial elements. Later, the nodule is composed of neuroglial elements only. The Purkinje cells of the cerebellum show swelling of the cytoplasm and lysis of the nucleus, and are reduced in number. The cortical neurons at times undergo chromatolysis. The leptomeninges, when their blood vessels are markedly parasitized, may show mobilization of macrophages and discrete infiltrations with lymphocytes.

The pathogenesis of some malarial symptoms and lesions is still obscure. Thus, abdominal symptoms, at times highly suggestive of appendicitis, or of some other acute condition, may appear in the course of acute malaria, either benign or malignant. The appendix, in some of these cases, shows heavily parasitized capillaries, but in others is normal. Also, since not all cases of clinical cerebral malaria present alterations in the brain at autopsy, the symptoms have been thought to be of toxic origin, yet a malarial toxin has never been demonstrated. An actual plugging of cerebral capillaries by the parasite is not a wholly adequate explanation of the cerebral lesions. That there is actual damage to capillary walls is indicated by the swelling of the endothelial cells, but this might be the result of direct damage by the accumulated parasites, or of anoxia from destruction of an excessive number of erythrocytes and impairment of the circulation.¹⁰⁵ Intravascular agglutination of erythrocytes has been seen in human and monkey malaria.¹⁰⁶ The malarial pigment alone may play an important part in the pathogenesis of some lesions⁹² since it can produce vascular damage (thrombosis and multiple hemorrhages) and renal degenerative changes in dogs when injected intravenously.

CHRONIC MALARIA.—In some cases the malarial parasite is able to maintain itself in the human organism for a long time, despite treatment. When the patient's resistance is diminished, from a number of causes, the protozoan undergoes multiplication and appears in the circulation. The course in these cases consists of irregularly spaced febrile attacks alternating with periods of latency. The condition may go on for years, and leads to chronic invalidism from anemia and cachexia. At autopsy there is great wasting and a sallow, muddy or subicteric tint to the skin. The most salient visceral finding is splenomegaly. The much enlarged malarial spleen (ague cake) may weigh as much as 2,000 grams. It is very firm, and cuts with increased resistance. The capsule is thick and usually covered by whitish nodular or plaque-like thickenings. There may be fibrous adhesions to neighboring structures. The cut surfaces are

dark gray or slaty, the pulp is very firm, and the malpighian bodies are inconspicuous. Microscopically, in advanced cases, there is thickening of the trabeculae and a fibrosis of the pulp, but earlier there is no fibrosis. Prominent black clumps of malarial pigment fill the cytoplasm and obscure the nucleus of macrophages throughout the pulp; to a much lesser extent it also occurs in reticulum cells of the lymphoid nodules. The latter are reduced in size and number. The liver is usually enlarged, dark gray or slaty, and firm. Malarial pigment forms dense black clumps within the enlarged Kupffer cells. The portal spaces are fibrosed and may contain increased numbers of lymphocytes, plasma cells, and pigmented macrophages. The existence of a true malarial cirrhosis is doubtful, although accepted by many authors. The liver cells are often laden with fat. The bone marrow, in sternal punctures, shows myeloid and erythroid hyperplasia, but this is less marked than in acute benign malaria.⁹⁴ The heart may be fatty, with tigering of the

nature of hematin or ferrihemic acid.¹⁰³ It is ultimately disposed of by being split within reticulo-endothelial cells into iron-containing hemosiderin and iron-free bilirubin. The latter accounts for the indirect van den Bergh reaction of blood plasma. It is excreted with the bile, and plays an important part in the production of thick bile and biliary dysfunction in the bilious remittent fevers. This, together with a reduction of cholesterol, explains the relatively frequent formation of gallstones in malaria.

Serum protein alterations are characterized by a reduction of the albumin fraction and an increase of the euglobulin. These changes probably explain the frequency with which the Wassermann reaction is positive in malaria. The rise in blood potassium at the time of the rigor apparently comes from the ruptured erythrocytes and from body cells in general, and may have a deleterious effect on the adrenal cortex.



Fig. 270.

Fig. 270.—Cerebral malaria. Multiple hemorrhages into brain; capillaries are found engorged with pigmented and parasitized erythrocytes. ($\times 180$.)

Fig. 271.—Cerebral malaria. The hemorrhages may be as numerous in the cerebellar cortex as in the cerebrum. The smaller blood vessels are laden with parasitized erythrocytes. ($\times 80$.)

myocardium, and the kidneys may be the seat of cloudy swelling. Rarely, symptoms of nephritis appear in the course of benign malaria, usually late in chronic cases. A nephrotic syndrome with subcutaneous edema, serous effusions, and albuminuria has been described, and is said to be more frequent in quartan malaria. In the autopsy reports available, there are mentioned inflammatory and proliferative alterations in the glomeruli, degenerative changes in the tubules, and inflammatory infiltrations in the interstitial tissue.¹¹³ The renal lesions bear no specific malarial characteristics.

Pathologic Physiology.—Malarial pigment is a decomposition product of hemoglobin, of the



Fig. 271.

Complications.—Cerebral malaria, excessive multiplication of parasites in the blood stream, and heart failure account for most of the deaths from malaria. Rare cases succumb to spontaneous or traumatic rupture of the spleen due to its great softening, while others present terminal clinical evidence of involvement of suprarenal glands or kidneys. Chronic cases may die of cachexia or of some pyogenic or bronchopneumonic complication. After recovery from the cerebral forms, important residua may remain in the form of pareses, paralyses, multiple sclerosis, and psychical impairment.¹⁰¹ Blackwater fever is considered separately.

Immunity.—There is both a natural and an acquired immunity to malaria, but the former

is probably of limited scope. The latter is both cellular and humoral. Defense seems to depend mainly on a parasiticidal effect that results in concentration of parasites in certain tissues, like the Billroth cords of the spleen and sinusoids of the bone marrow and liver, where they are destroyed by reticulo-endothelial cells. After repeated relapses a strong tolerance or an actual immunity is developed; at the beginning this depends on the presence of parasites (premunition) in the body, even though all symptoms have disappeared. Malarial immunity is strictly specific, so that reinfection is possible with a different species or strain of the malarial parasite.

BLACKWATER FEVER

General Character and Etiology.—Blackwater or hemoglobinuric fever is a dangerous complication of malaria, characterized clinically by an abrupt onset with a severe chill, fever, bilious vomiting, jaundice, the sudden passage of dark red or blackish urine, and a rapidly developing anemia.

The geographic distribution follows that of malaria, but its occurrence is more variable and spotty; in some malarious countries it is practically unknown. It is most frequent in hyperendemic regions, and is almost exclusively connected with falciparum malaria, and with rural, rather than urban, conditions.

The cause of the hemolytic crisis that characterizes the disease is unknown. Five main theories have been proposed, explaining it (1) as being a disease *sui generis*, caused by a specific etiological agent other than the malarial parasite; (2) as provoked by a strongly hemolytic strain of malaria; (3) as a quinine effect; (4) as an allergic or anaphylactic reaction; and (5) as the result of autoagglutination of erythrocytes, leading to intravascular hemolysis, and resulting from immunization of the host against an isoagglutinogen-like substance that may be present in the malarial parasite. There is no evidence in support of the first two theories. As regards quinine, its relation to hemoglobinuric fever seems certain in many cases, but the mode of action is obscure, and there are undoubtedly instances of the disease appearing without the administration of quinine. It seems that the syndrome is most frequent among nonimmune or partially immune individuals under irregular or insufficient treatment. There is not enough evidence for acceptance of the allergic theory. The theory of the appearance of autoagglutinins in this disease¹¹⁰ has received some experimental support from finding that a polysaccharide isolated from various animal parasites inhibits the alpha and beta agglutinins in human sera, and that a few sera tested, from blackwater fever patients, have shown an increased alpha isoagglutinin titer.¹¹⁵ The possibility thus exists that the malarial parasite may contain an isoagglutinogen-like substance that induces the formation of agglutinins that act on the host's erythrocytes.

Pathogenesis and Pathologic Anatomy.—The hemolytic crisis manifests itself by the passage of dark urine shortly after the rigor, or before it. Fever follows the rigor and is highest

at the beginning of the hemoglobinuria, diminishing as the urine clears. There may be one or several attacks of hemoglobinuria over a period of a few days or of several weeks. Jaundice appears with the attack, but not infrequently precedes it, intensifying in accordance with the gravity of the hemolytic crisis. Some suppression of urine is common at the beginning of the attack, the output increasing as the urine clears. In many cases, however, oliguria develops and may go on to anuria, which is almost invariably fatal. The average mortality in blackwater fever is probably about 25 per cent.

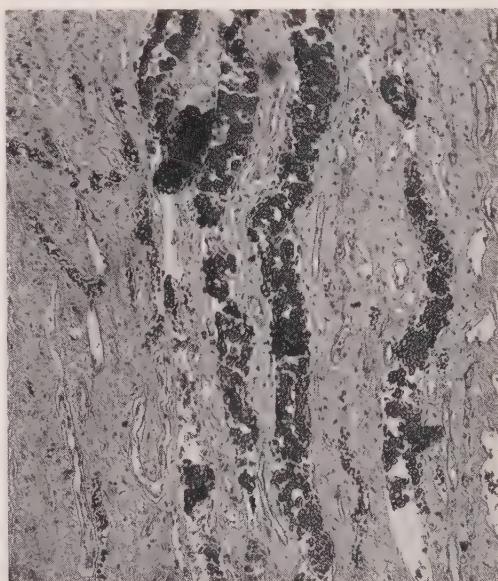


Fig. 272.—Blackwater fever. In this case there was an extraordinary filling of renal collecting tubules with hemoglobin derivatives and debris. ($\times 80$). (Tissue by courtesy of Dr. I. Rivera Lugo, Puerto Rico.)

The gross postmortem findings comprise more or less intense jaundice, evidences of malaria, mostly as enlargement and pigmentation of the spleen and liver, renal alterations, and the effects of anemia.

The kidneys are large and swollen. Externally and on section, they are dark brown, at times violaceous. A greenish tint is evident when the jaundice is intense. On section, the markings are blurred and the swollen cortex is poorly demarcated from the medulla. The pyramids are much darker than the cortex. Microscopically the alterations are almost exclusively tubular. The ascending loop of Henle and the convoluted tubules, particularly the distal, are the seat of marked degenerative changes. The cytoplasm of the cells lining the tubules may contain fat droplets, but more frequently there are found in it hyaline droplets, some of which probably represent hemoglobin. In some of the cells the portion toward the lumen is cast off, so that the tubule appears wider than normal; an actual dilatation is also evident at times. Within the convoluted and

collecting tubules, particularly the latter, there are pink and brown amorphous masses of blood pigment and degenerate or necrotic epithelial cells, while the collecting tubules contain hemoglobin casts, in addition (Fig. 272). The contents of the tubules are variable in amount, and may be scant, even in severe cases. The glomerular capillaries are empty, but no other change is discernible in the glomeruli. The blood vessels are normal, except for congestion, particularly of the medulla, and most marked in cases of anuria. Pigment and parasites are rarely demonstrable in this organ, but hemosiderin may be found within the lumen of tubules and in their lining cells.



Fig. 273.—Chronic balantidial colitis. Deeply undermined ulcer, with Balantidium forming a colony, and also extending singly as far as subserosa. Round-celled infiltration about ulcer, and edema of submucosa. ($\times 40$.)

The spleen and liver are large, and may show malarial pigmentation. The microscopic picture may be as described for malaria, except that parasites may not be found, and malarial pigment may be very scanty. In the liver the bile capillaries are filled with bile, and there is central necrosis of lobules. The reticuloendothelial cells of the spleen, liver, and bone marrow contain pale yellow, refractile, hemosiderin pigment. The heart is often soft and fatty. The bone marrow undergoes hyperplasia of normoblastic type.

The ultimate cause of the anuria is unknown. It was long thought to be due to mechanical plugging of renal tubules by blood pigment casts and deposits,¹⁰⁹ but there are cases in which no tubular obstruction is found at autopsy. A primary damage to the distal convoluted tubule

from saturation with acid or basic radicles, or indirect damage due to the anemia and to alterations of renal blood flow have been postulated.¹¹⁴ It is interesting that similar or identical pathologic changes are found in the kidney in other conditions, such as the crush syndrome (see page 588).

Balantidiasis

Balantidium coli is a large ovoid organism measuring 50 to 80 microns in length and 40 to 60 microns in width, in the vegetative or trophozoite form. It possesses a pellicle bearing short cilia, and contains within its endoplasm a large kidney-shaped macronucleus and a much smaller spherical micronucleus. The cysts are ovoid or spherical, and have a diameter of 45 to 65 microns; they possess a doubly-contoured wall and nuclei like those of the trophozoites. This is a cosmopolitan parasite, mostly of pigs, but it may also be found in higher and lower apes, and in rats. Man is occasionally infected by ingestion of the cysts.

The parasite may rarely be encountered in the feces of healthy people. In a small proportion of cases it may instigate a severe diarrhea or dysentery, which at times proves intractable, and may terminate fatally from exhaustion, intestinal hemorrhage, or perforation of the colon and peritonitis. The bowel lesions are very similar to those of amebic colitis in their location and gross and microscopic appearance. There is a marked tendency to undermining of the margin of the ulcers in chronic cases, and extensive blackish areas of necrosis and gangrene may develop in the acute infections. Microscopically, a zone of coagulation necrosis is visible in the base and margins of the ulcer, while the submucosa in its neighborhood is edematous and infiltrated with lymphocytes, monocytes, and plasma cells that also extend to the muscle coat and subserosa. Neutrophiles are usually scanty or absent (Fig. 273). While the balantidia are seen mostly in the mucosa and submucosa of the affected portions, they may spread to all coats, ahead of the margin of spreading ulcers; they may be scarce and difficult to identify, particularly in the presence of autolytic changes. Although they are often seen within veins and lymphatics of the colonic wall, abscess of the liver has not been found as a result of balantidial colitis.

HELMINTHIC DISEASES

The Distomases or Distomatoses

Hepatic Distomiasis.—This is caused, mostly, by the trematodes *Fasciola hepatica* (the sheep liver fluke), *Clonorchis sinensis* (the Chinese liver fluke) and *Opisthorchis felineus* (the cat liver fluke). *Dicrocoelium dendriticum* is the cause of human distomatosis with some frequency in Rumania and Turkestan, but is very rare elsewhere.

Pathologic Anatomy.—When very numerous, the metacercariae of *Fasciola hepatica* may produce severe damage to the liver, as they cross this organ in search of the bile ducts, giving rise to multiple areas of necrosis. As a rule,

however, the main damage produced by the above three flukes is to the bile ducts (Fig. 274). The parasites induce epithelial hyperplasia and adenomatous proliferation, accompanied by periductal infiltration with eosinophiles, lymphocytes, and plasma cells, and by a progressive fibrosis of the portal spaces. In opisthorciasis the parasite may be found in the pancreatic ducts. The liver enlarges, but only rarely does a true cirrhosis ensue. The symptoms are vague, consisting of fever and atypical gastrointestinal, vesical, and hepatic manifestations, usually with eosinophilia. In severe and advanced cases there may be tachycardia, dizziness, and mental depression. The corresponding diseases are known, depending on the causative parasite, as fascioliasis, clonorchiasis, and opisthorciasis.

edema of face and legs are frequent signs and symptoms. In grave cases these features progress to anasarca, marked toxemia, vomiting, prostration, and death. Eosinophilia is usually present.

Pulmonary Distomiasis.—*Paragonimus westermani*, the Oriental lung fluke, is ovoid, thick, and reddish-brown; it measures 7.5 to 12 mm. in length, 4 to 6 mm. in breadth, and 3.5 to 5 mm. in thickness. The eggs are broad, ovoid, brown, and operculate; they average 85 by 55 microns. The habitat of the adult worms is in pulmonary cavities, from which the ova pass to the outside with the sputum or with the feces when sputum is swallowed. After two to seven weeks in water a miracidium is hatched which penetrates snails, mostly of the genus *Melania*, for metamorphosis

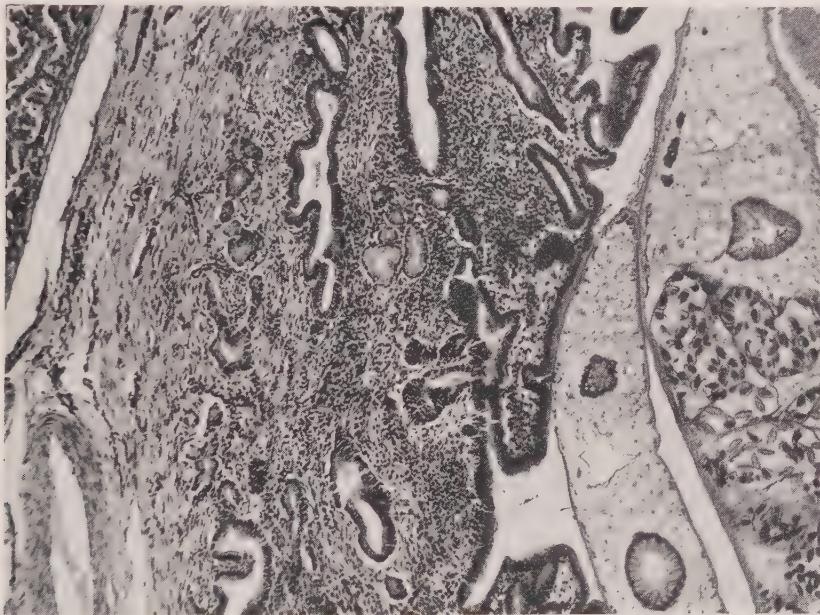


Fig. 274.—*Clonorchis sinensis* within dilated intrahepatic bile duct. Adenomatous proliferation and marked round-cell infiltration in wall of duct; fibrosis of portal space. ($\times 80$.)

Intestinal Distomiasis.—*Fasciolopsis buski*, the large intestinal fluke, is ovoidal and elongate. It is distinctly larger than the other flukes parasitic in man, varying from 20 to 75 mm. in length, 8 to 20 mm. in breadth, and 0.5 to 3 mm. in thickness. The eggs and life cycle are like those of *Fasciola hepatica*. The infection, which is limited to the Far East, is acquired by ingesting aquatic vegetation. The metacercariae encyst in the duodenum, then attach themselves to the mucosa of the duodenum and upper jejunum. Less frequently, they may be found fixed to the wall of the colon.

Points of ulceration at the site of attachment, intestinal hemorrhage from these areas, and abscess formation in the wall of the intestine, are the main pathologic lesions. Abdominal pain, at times suggestive of gastric or duodenal ulcer, diarrhea and subcutaneous

and multiplication. The cercariae, on leaving the snails, enter crayfish or crabs, in which the metacercariae encyst in the muscles or viscera. Man is infected by eating the second intermediate hosts. The metacercariae encyst in the duodenum, and reach the lungs by wandering across the wall of the duodenum, peritoneal cavity, diaphragm, pleural cavity, and pleura. They mature within cystic spaces that develop about them next to bronchioles. Paragonimiasis, or endemic hemoptysis, is found in the Far East, the Philippines, parts of Africa, and Brazil, Peru, and Venezuela. The parasite has been found in the United States in cats, dogs, and pigs, but no autochthonous cases have been encountered.

Beginning insidiously the disease goes on to a state of chronic cough, recurring hemoptysis, and thoracic discomfort. While anemia may develop from repeated pulmonary hemorrhages,

systemic manifestations are often lacking. Pulmonary osteoarthropathy may be well-marked in old cases.

In the lungs the worms are surrounded by a zone of infiltration with eosinophiles, polymorphonuclears, and round cells, about which a fibrous capsule develops. The worms lie in a space or tunnel containing rusty-colored fluid resembling anchovy sauce which, when coughed up, constitutes a type of sputum very characteristic of the disease. Its color is due to the large number of brown eggs, erythrocytes, and eosinophiles that it contains. The cavities are most numerous in the peripheral parts of the lungs. Together with the surrounding zones of inflammation and fibrosis they form nodules that average about 2 cm. in diameter, with a space or tunnel in the center; adjacent spaces may coalesce and form larger cavities. Besides the lung, other organs, such as the brain, intestine, peritoneum, liver, testes, muscles, and skin, may present bluish, cystic cavities or tunnels containing the fluke.

Diseases Due to Trematodes

SCHISTOSOMIASIS OR BILHARZIASIS

Etiology and Life Cycle.—The most important schistosomal diseases of man are the vesical or urinary, due to *Schistosoma haematobium*, Manson's or the intestinal, due to *S. mansoni*, and the Japanese or Asiatic, due to *S. japonicum*.

The female worm is slender and cylindroid, while the male is shorter and has a central trough, the *gynecophoral canal*, that enfolds part of the female during copulation. The females range from 10 to 25 mm. in length and from 1.5 to 3 mm. in diameter. The ova of *S. haematobium* average 150 by 50 microns and are oval and have a terminal spine. The mansonic eggs, approximately the same size, are also oval, but with a lateral, well-developed spine. The *S. japonicum* ova average 85 by 57 microns, are oval or rounded, and have a lateral and subterminal hooklet that is very small and inconspicuous.

DEVELOPMENT IN SNAIL.—Man is the principal definitive host of *S. haematobium* and *S. mansoni*, but other mammals are also found naturally infected with *S. japonicum*. Various species of snails are the intermediate hosts. The ova that are passed with the urine or feces of the mammalian hosts must reach water if the parasite's life cycle is to be completed. A free-swimming *miracidium* is then hatched which penetrates snails of certain species, within which it undergoes metamorphosis into first and second generation *sporocysts*, with the formation of extremely numerous *cercariae* within the latter. In due time, the fork-tailed cercariae, the infective form of the schistosomes, emerge from the snail. This requires approximately four to six weeks in the case of *S. haematobium*, three to four for *S. mansoni*, and five to seven for *S. japonicum*.

INVASION OF MAN.—When man comes in contact with water infested with cercariae, these readily penetrate through the skin or mucous membranes, only the body going in while the tail drops off into the water (Fig. 275). From this moment, and until it grows to the adult

form, the invading parasite is known as a *metacercaria* or *adolescaria*. They enter venules in the derma, and are carried with the blood through the right side of the heart and along pulmonary arterioles to the left side of the heart, whence they are ejected with the arterial blood to all organs and tissues. Those reaching abdominal viscera drained by the portal vein pass the capillary net to the venous side and gather in intrahepatic portal branches where they mature. All others either repeat the cycle or are caught as emboli in blood vessels, die, and are absorbed.

HABITAT IN MAN.—After attaining maturity within the liver the worms travel against the blood stream to tributaries of the portal vein in the abdominal and pelvic cavities. Some unexplained tropism has adapted *S. haematobium* to pelvic plexuses, especially the vesical (although it may be found in mesenteric veins), while *S. mansoni* and *S. japonicum* prefer the hemorrhoidal plexus and the colonic and mesenteric veins. The *haematobium* worms first reach the hemorrhoidal plexus, some going to the rectum for oviposition, while most of them pass on to pelvic plexuses.

OVIPOSITION.—After copulating in the larger veins, the paired worms, or the gravid female alone, advance into small visceral branches that fit the female snugly. The ova are deposited in these branches one by one in the case of the mansonic parasite and in rows in the case of the other species. This takes place mostly in the submucosa of the urinary bladder and distal portions of the ureters in urinary bilharziasis, and in the mucosa and submucosa of the sigmoid colon and rectum (Fig. 276) in the mansonic and Asiatic diseases.

EXTRUSION OF EGGS.—The actual manner in which the eggs leave venules to pass into the lumen of the intestine or the cavity of the urinary bladder is unknown. Some of the factors invoked, alone or in combination, have been the following: Piercing of the wall of venules by the spine; weakening of the wall from irritation produced by the eggs, or an actual lysis by secretions contained in the embryo; expulsion by the rise of pressure within the venule due to plugging by the female worm or by the restitution of blood flow when the worm withdraws; and the effect of compression by the peristaltic movements or by the passage of the feces down the lumen.^{128, 129, 137} Evidence has been adduced showing that most ova are trapped in situ by the inflammatory reaction and pseudotubercle formation they instigate, and that the eggs soon become covered by endothelium that extends from that lining the venule, so that very probably only those reaching the most superficial parts of the mucosae can ever get to the outside.^{137, 138} In urinary bilharziasis eggs appear in the urine one to three months after infection, while in the mansonic the interval is 37 to 42 days, and in the Asiatic, 30 to 70 days. The life cycle is completed when eggs reach water and infect snails of the appropriate species.

Epidemiology.—The urinary disease occurs mainly in Africa: Mediterranean littoral, Ethiopia, Anglo-Egyptian Sudan, the east coast down to South Africa, Madagascar, Mauritius, Reunion, Central Africa, and the Gold Coast from Senegal east to Lake Chad and south to French Equatorial Africa. There are minor

foci in the Middle East (Syria, Palestine, Iraq, and Arabia), as well as in southern Portugal and Greece, and in Cyprus.

Manson's bilharziasis, originally African, was brought to the Caribbean region and South America by Negro slaves. In Africa it occurs in the Nile Delta, Anglo-Egyptian Sudan, the east coast from Zanzibar to below the Zambezi River, Madagascar, and Central Africa. Scattered foci are present in Senegal, French Guinea, and east to Lake Chad. Cases have been reported from other points in south, west central, and north Africa. There is a small focus in Yemen, Arabia. In South America it is present in northern Venezuela, Dutch Guiana, and northern Brazil. In the Caribbean it is found in Santo Domingo,¹⁴¹ Puerto Rico, Vieques, St. Martin, St. Kitts, Nevis, Montserrat, Antigua, Guadeloupe, Martinique, and St. Lucia.

Japanese schistosomiasis is limited to the Far East: China, where millions are affected in the Yangtze River Valley, Formosa, Japan, Philippine Islands, and Palœ District of Celebes.

Man is the main reservoir for the urinary and masonic forms, while the Oriental parasite frequently infects field mice and domestic mammals. The propagation of the disease depends on the following: (1) The presence of human beings, or domestic animals that are passing eggs with the urine or feces; (2) the presence of snails of certain species in streams, rivers, ponds, lakes, irrigation canals, ditches, and rice fields; (3) the pollution of these waters with infested urine or feces directly by the mammalian hosts or indirectly through improper disposal of sewage; and (4) the exposure of the victim by wading, bathing, or otherwise coming in contact with infested water. An important source of the infection among snails in the Orient is the use of human

excreta as a fertilizer in vegetable fields. Infection by drinking, with the cercariae penetrating through the buccal, pharyngeal, or esophageal mucosa, is probably of frequent occurrence in certain parts of Africa. The intermediate molluscan host varies for each of the three schistosomes. For *S. haematobium*, several species of the genus *Bulinus* are the important intermediaries. *S. mansoni* utilizes several species of the genus *Planorbis* in Africa, *Australorbis glabratus* in the Caribbean region and Venezuela, and in Brazil the very similar, if not identical, *A. olivaceus* and *A. centimetralis*. *Tropicorbis havanensis*, which occurs in the United States, has lately been found suitable, experimentally, to act in that capacity.¹³¹ *S. japonicum* utilizes various species of *Katayama* and *Oncomelania*.

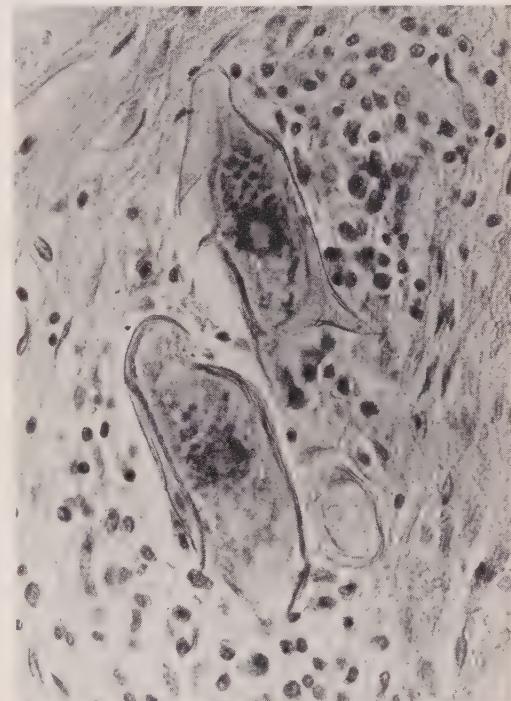
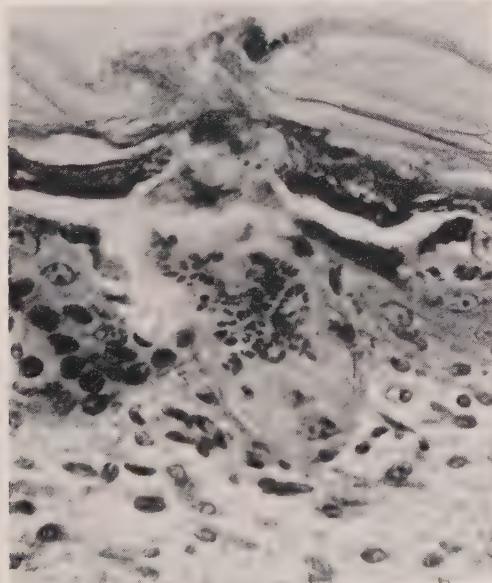


Fig. 276.—Manson's schistosomiasis. Early leucocytic infiltration about two newly laid ova in rectal submucosa; embryos are well preserved, and the lateral subterminal spine is well shown in ovum to right. (X360.)

In most of the endemic foci it is difficult or impossible for the inhabitants to avoid infection, since they must work in the infested waters or utilize them for bathing and domestic purposes. The infection is usually contracted in childhood or early youth; in all forms it is infrequent after 40 years of age. The rate of incidence depends on the opportunities for exposure, and is determined by the habits and occupations of the community in their relations to the bodies of infested waters.

Pathogenesis and General Pathology.—The basic pathologic changes in man, and the fundamental pathogenetic factors, are the same for

Fig. 275.—Manson's schistosomiasis. Cercaria in the act of traversing epidermis after having dropped its tail. Experimental infection of rabbit. (X450.)



Similar changes occur in the distal third of the *ureters* in most cases. They lead to obstruction, with dilatation of the proximal portions, hydronephrosis, hydronephrotic atrophy of the kidneys, and suppuration if bacterial infection supervenes. Small papillomata may form in the renal pelvic mucosa.

COMPLICATIONS.—In about 8 per cent of cases, calculi develop in the bladder, renal pelvis or ureters, and are composed of deposits of uric acid, oxalates and phosphates about a nucleus made up of ova and cellular debris. There may develop fistulas to the bladder, or between urinary or genital organs and the intestines. Sarcoma is much less frequent than carcinoma as a complication. Rarely the bladder may rupture into the peritoneal cavity.

Manson's Schistosomiasis.—The organs more commonly affected in the course of this disease are the colon, liver, spleen, and lungs.

In the *colon* the distal parts are more frequently and severely involved. Frank ulceration is rare. Congestion of the mucosa and thickening of the wall due to edema and fibrosis of the submucosa are the main findings in advanced cases, but punctate hemorrhages and finely granular or sandy patches may also be seen in the mucosa. In old infections with minimal intestinal manifestations there is little or no gross involvement of the mucosa. The eggs are most numerous in this coat and in the submucosa. In the former they lie within venules or in their immediate vicinity; many of these are empty shells and evoke no reaction on the part of the tissues. The number of eosinophiles and plasma cells in the mucosa is usually increased. In the submucosa, pseudotubercles develop about the eggs, accompanied by eosinophiles and round cells. At times an intense and diffuse infiltration with eosinophiles is found in both these coats. Pseudotubercles may also appear in the muscle coat and subserosa, at times forming clusters in the latter coat, and visible grossly as pearly gray, sharply outlined, and glistening nodules. Granulation tissue forms in the submucosa in severe cases. In old infections, fibrosis of the submucosa, particularly in the rectum, is the main finding.

Papillomata are a frequent and important feature of the disease in Egypt, usually appearing first in the rectum, later in more proximal parts, and even in the small intestine in a few cases. They range in diameter from 1 or 2 mm. to about 5 mm., less frequently attaining a size of 4 and even 8 cm.; the larger ones are multilobulated. They may be pedunculated or sessile, and are dark red or brown, and soft, with an uneven, easily bleeding surface. They are composed of highly vascularized connective tissue in which are found eggs, eosinophiles, and lymphocytes, and which is covered by mucous membrane that often is superficially ulcerated. Flat elevated masses may project from the mucosal surface, and consist of areas of more marked fibrosis of all coats. The *small intestine* is rarely involved grossly; microscopically, ova and pseudotubercles may be found in the mucosa and submucosa in the heavier and older infections.

The *liver* changes are mainly portal. Ova swept from the colon with the venous blood

are detained mostly in the portal spaces, less frequently reaching the sinusoids. Pseudotubercles form about them, eosinophiles and round cells appear about these nodules and also more diffusely, and the connective tissue of the portal spaces gradually and slowly increases. The fibrous tissue, highly vascularized at first, later becomes dense, collagenous, and white. By this time the fibrosis has extended to the smaller portal spaces and a true cirrhosis has developed, with proliferation of bile ducts and formation of pseudolobules. Brown granules of schistosomal pigment are taken up by the enlarged Kupffer cells and by histiocytes in the portal spaces.

Grossly the organ is large during the intermediate stage, but begins to contract as the fibrosis progresses. The surface rarely shows more than a fine nodularity and a diffuse whitish thickening of the capsule. Minute pale yellow or white nodules may be seen beneath the capsule and on section. The consistency is distinctly increased. Rarely, the grayish cast of bilharzial pigmentation is in evidence. On section the most distinctive feature is a periportal fibrosis about the larger venous branches (Fig. 278), rapidly diminishing toward the smaller portal spaces. When well developed, the larger portal veins are surrounded by pinkish or white collars of fibrous tissue, this constituting Symmer's pipe-stem type of cirrhosis, which is highly characteristic of the disease. Jaundice is rarely seen.

The *spleen* enlarges, and frequently weighs 1,000 grams or over in old and severe cases. Early in the course the consistency is normal and the pulp red. Later it becomes dense and rubbery. The capsule thickens and may be covered by fibrous adhesions. On section the pulp is pale because of diffuse fibrosis, the trabeculae are thick, and the lymphoid follicles inconspicuous. A chocolate or gray color from pigmentation is more frequently seen in the intermediate than in the late stage. The microscopic alterations in the intermediate stage consist of congestion, increase of the splenic tissue, and deposition of brown pigment in reticulum cells of the red pulp. Late cases show a diffuse fibrosis of the pulp and a diminution in the size and number of the malpighian corpuscles. Pigment may be scanty, or absent, in old infections. At times, numerous eosinophiles are seen throughout the pulp. Ova and pseudotubercles are less frequently found in this organ in America than in Egypt.

There are two ways in which the *lungs* become involved. In one of these, which is the more frequent, small grayish or white nodules averaging 1 mm. in diameter are visible or palpable beneath the pleura and on section throughout the pulmonary tissues, or at a few points only. They represent groups of pseudotubercles about eggs that have been transported with the circulation, probably by way of the hemorrhoidal plexus and inferior vena cava. In the second type of involvement, much less frequent than the above, the numbers of ova reaching the lungs is greater, so that the gross appearance may be suggestive of miliary tuberculosis. In addition there are raised dark red or purplish patches of consolidation measuring up to 1 cm.

in diameter, and yellowish foci about 0.2 cm. across. The parenchyma is intensely congested and edematous. Microscopically there are pseudotubercles, patches of intense eosinophilic infiltration of the alveoli about dead worms, at times with hemorrhage, and arterial lesions provoked by the ova. The eggs, which average 150 by 50 microns, arrive in the lungs as emboli and obstruct small arteries; a pseudotubercle is produced and the intima becomes thickened by fibrosis. To compensate for the obstruction to the flow of blood, vascular proliferations or "angiomatoids" develop (Fig. 279). The increased pressure in the pulmonary circuit, resulting after a time from the multiple vascular injuries, induces a diffuse intimal sclerosis that extends from the smaller to the larger arterial branches. The right side of the heart hypertrophies and fails, so that, clinically, cyanosis and other signs of myocardial failure are prominent and may overshadow the hepatic cirrhosis. The condition is another form of Ayerza's disease.¹⁴³

or pedunculated polyps, usually not over 1 cm. long, are frequently found projecting from the mucosa, mostly in the sigmoid and rectum. On section, yellow or brown foci of softening are seen in the submucosa, and represent pseudo-abscesses about large groups of eggs (Fig. 280). The mesenteric and retroperitoneal lymph nodes are moderately enlarged, and pale or brown on section; in older infections they undergo fibrosis. The distal portions of the ileum are rarely involved grossly, and only in very severe cases.

The liver and spleen are affected in the same manner as in Manson's bilharziasis. The lungs may contain eggs surrounded by large numbers of eosinophiles, and by pseudotubercles.

At autopsy, in advanced cases, the principal gross findings are emaciation; pallor; a large or contracted liver with marked periportal fibrosis; splenomegaly with fibrosis of the pulp; serous effusions, mainly ascites; whitish nodules over the colonic peritoneum; fibrous thickening and rigidity of the wall of the colon, with small

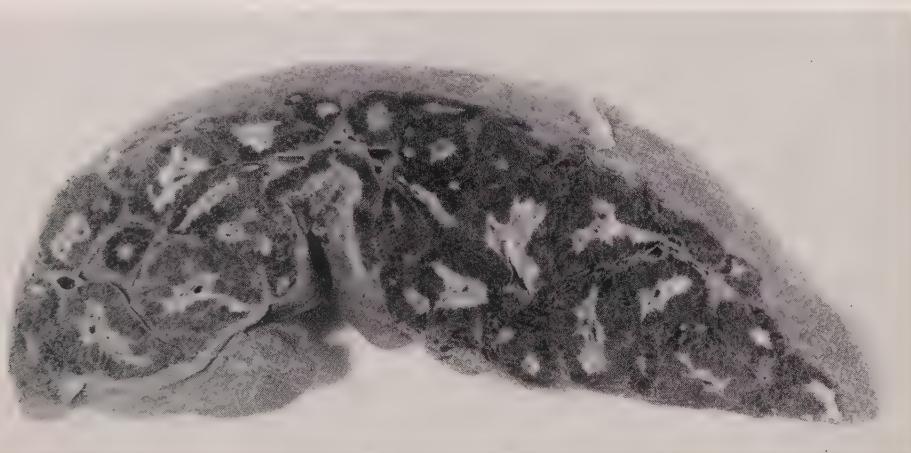


Fig. 278.—Manson's schistosomiasis. Hepatic cirrhosis of "pipistem type" in case of advanced schistosomiasis.

Asiatic Schistosomiasis.—The colon, liver, spleen, mesentery, and peritoneum are the organs and tissues more severely affected in this disease.

The colon is more severely affected in the sigmoid and rectum, but in the heavier infections its whole length is involved, up to the cecum. Gross alterations are more often in evidence at autopsy than in the mansoni form, with a greater fibrosis of the submucosa that extends also to the muscle coat and subserosa, giving the walls an increased thickness and a considerable rigidity. The thickening is more marked along the mesocolic attachment. The omentum is thickened, fibrotic, rolled up on itself, and often adherent to the colon. Whitish, yellowish, or gray nodules 1 to 4 mm. in diameter project from the serosa of the colon at various levels; they represent groups of pseudotubercles. The mucosa shows congestion, small points of hemorrhage and, in some cases, superficial ulcers. Small dark red, and flat

polyps projecting from the mucosa, and thickening and fibrosis of the omentum.

Microscopically this form of the disease differs from the mansoni mainly in that the larger number of ova deposited in the tissues, and swept by the blood into other organs, principally the liver, brings about a more violent reaction on the part of those tissues. Large numbers of eosinophiles appear about the ova, which are laid in groups or rows. These collections, when in the intestinal mucosa, often break into the lumen through a minute opening, and the resulting cavity may later be lined by columnar epithelium that extends inward from the surface. A similar reaction, less violent, obtains in the portal spaces, retarding the development of the pseudotubercles. Otherwise, tissue changes are as in Manson's schistosomiasis.

COMPLICATIONS.—In the mansoni disease approximately one-third of the fatal cases succumb

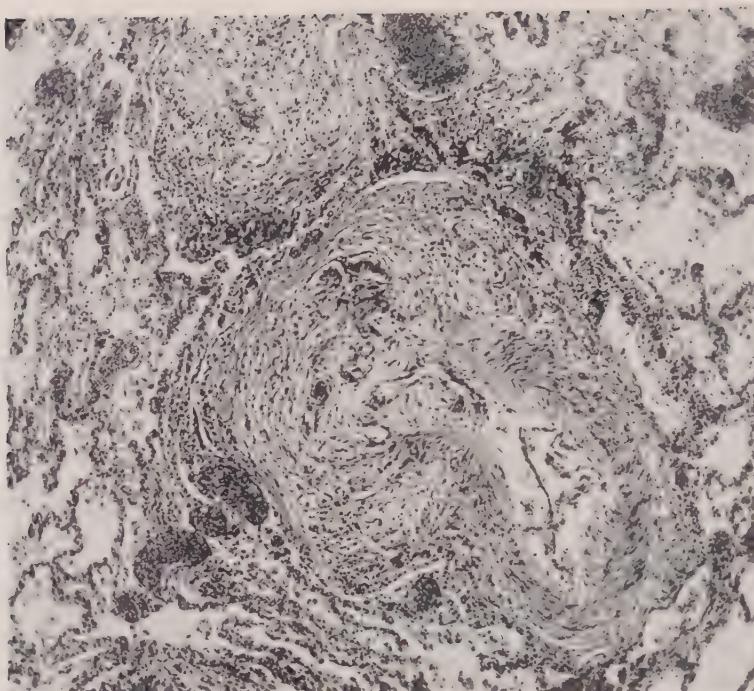


Fig. 279.—Manson's schistosomiasis with advanced pulmonary involvement. Early "angiomyoid," secondary to obstruction of branches by eggs arriving as emboli. ($\times 80$.)

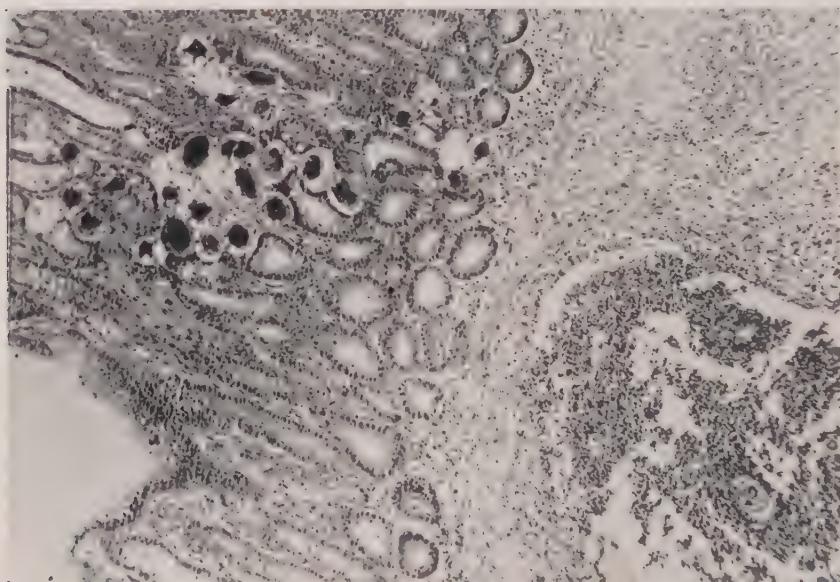


Fig. 280.—Oriental schistosomiasis. Colon of dog experimentally infected. Many egg-shells, mostly calcified, in mucosa; pseudoabscess in submucosa. ($\times 80$.) (Section by courtesy of Professor Ernest C. Faust.)

to hemorrhage from ruptured gastroesophageal varices, one-third to cachexia from hepatic cirrhosis, and another third to complications referable to the disease itself or to intercurrent illnesses. Adenocarcinoma of the colon is more frequent among the infected than in the general population. Most individuals with Japanese schistosomiasis die of cirrhosis and cachexia, or of intercurrent diseases.

SWIMMER'S ITCH

This is a dermatitis resulting from exposure to cercariae of various animal schistosomes. It is met with in various parts of Occidental Europe, the Federated Malaya States, Mexico, Colombia, Canada, and the United States. In this country, it is most frequent in Wisconsin, Michigan, Minnesota, and Iowa. The definitive hosts of these schistosomes are mostly birds.

The cercariae, which are found in fresh water, penetrate the skin, producing an infiltration with polymorphonuclears and lymphocytes, followed by eosinophiles. Clinically, there is severe itching, after which urticaria develops, to subside in about one-half hour, white spots remaining in place of the wheals. Several hours later a prickling sensation begins and papules develop, some of which may become infected from scratching. The average duration is about one week, if uncomplicated by marked bacterial infection. Drying of the film of water on the bather's body stimulates the cercariae to penetrate. None of these cercariae can penetrate beyond the skin.

Diseases Due to Platyhelminthes (Cestodes or Tapeworms)

TAENIASIS SOLIUM AND CYSTICERCOSIS

Etiology and Life Cycle.—The adult *Taenia solium* lives in the small intestine of man, the definitive host, with its head or scolex attached to the mucosa. As its name implies, it is usually solitary, rarely there being two or more worms. When fully grown it measures 2 to 7 meters (about 7 to 23 feet) in length. The *scolex*, 1 mm. in diameter, is characterized by the rounded *rostellum*, which is armed with a double row of 22 to 32 hooklets, and by four deep, round suckers. The neck is 5 to 10 mm. long and about 0.5 mm. broad. Next come the immature proglottids or segments, which are broad and short, then the mature ones, larger and square, and lastly, the gravid segments, about twice as long (12 mm.) as they are broad. The eggs, like those of *T. saginata* and *T. echinococcus*, are spherical or nearly so, yellow or brown, and 30 to 40 microns in diameter; the thick shell surrounds a thin and hyaline membrane that contains a hexacanth embryo, so-called because of its three pairs of hooklets.

The eggs passed by man with the feces are swallowed by the intermediate host, usually the hog. The embryo or *oncosphere* which is liberated in the small intestine of this animal, penetrates venules in the intestinal wall and is transported in the blood to various organs and tissues, where it encysts and is known as a *cysticercus* (*Cysticercus cellulosae*), representing

the larval form of the parasite. This consists of a clear, glistening, and ovoid bladder, some 5 mm. long and 10 mm. broad, with an invagination on one side that contains a white spot, the head or *scolex* with its hooklets.

Epidemiology.—*Taeniasis solium* is cosmopolitan in distribution. Man acquires the intestinal infestation by ingestion of viable cysticerci in undercooked pork. The cysticercus, on the other hand, develops in the tissues of man when he ingests ova in water or food contaminated with the excreta of a person that carries the intestinal parasite. Also, individuals harboring a tapeworm may convey the ova to their mouths with soiled fingers. Last, it is possible that autoinfection may take place in some cases when ova or ripe proglottids are carried to the stomach or duodenum by reverse peristalsis.

Pathogenesis and Pathologic Anatomy.—The adult worm in the intestine produces little harm and but few symptoms, if any. There may be disorders of the appetite and of digestion, and either occasional diarrhea or constipation.

The larval form produces a disease, cysticercosis, which may be of serious import when the brain is involved. The tissues and organs affected, in order of frequency, are the subcutaneous tissue, brain, orbit, muscles, heart, liver, lungs, and peritoneum, but the larval cysts may develop in any part of the body. Symptoms depend on the number and location of the cysticerci. Epilepsy and other mental disturbances are important manifestations of cerebral cysticercosis. When appearing without antecedents in an adult who has lived in or visited countries where taeniasis solium is known to occur, epilepsy should suggest searching for subcutaneous nodules by palpation, and for calcified cysticerci in muscles and organs roentgenographically.^{145, 148}

The cysticerci are round when situated in viscera and serous membranes, while in the musculature and subcutaneous tissue they are elongated by compression. They average 2 to 5 mm. in diameter, and while alive appear as small glistening cysts with a white spot. After death of the larva the cyst becomes opaque. Microscopically, while the larva is alive there is little more than slight lymphocytic infiltration and compression of the surrounding tissues. After death of the larva the cyst is surrounded by a zone of infiltration with polymorphonuclears, lymphocytes, vacuolated macrophages, epithelioid cells, and a few foreign-body giant cells. This is surrounded by a zone of fibrosis and plasma cell infiltration, with a ring of congestion and infiltration with plasma cells and lymphocytes. Later the contents of the cyst degenerate into a pink amorphous mass, and are surrounded by a barrier of epithelioid and giant cells about which there is a zone of lymphocytic infiltration and fibrosis. Lastly, the cystic area is replaced by fibrous tissue, or it undergoes calcification.

In the brain, the cysts are found projecting from the leptomeninges and into the ventricles, as well as throughout the cerebral substance (Fig. 281). They are more numerous in the leptomeninges, particularly at the base and along the sylvian fissures. Microscopically,



Fig. 281.—Cerebral cysticercosis. The larval cysts may still be seen within some of the cavities, while they have dropped out of others. (Courtesy of Armed Forces Institute of Pathology and Ash and Spitz: Pathology of Tropical Diseases, W. B. Saunders Co., 1945.)

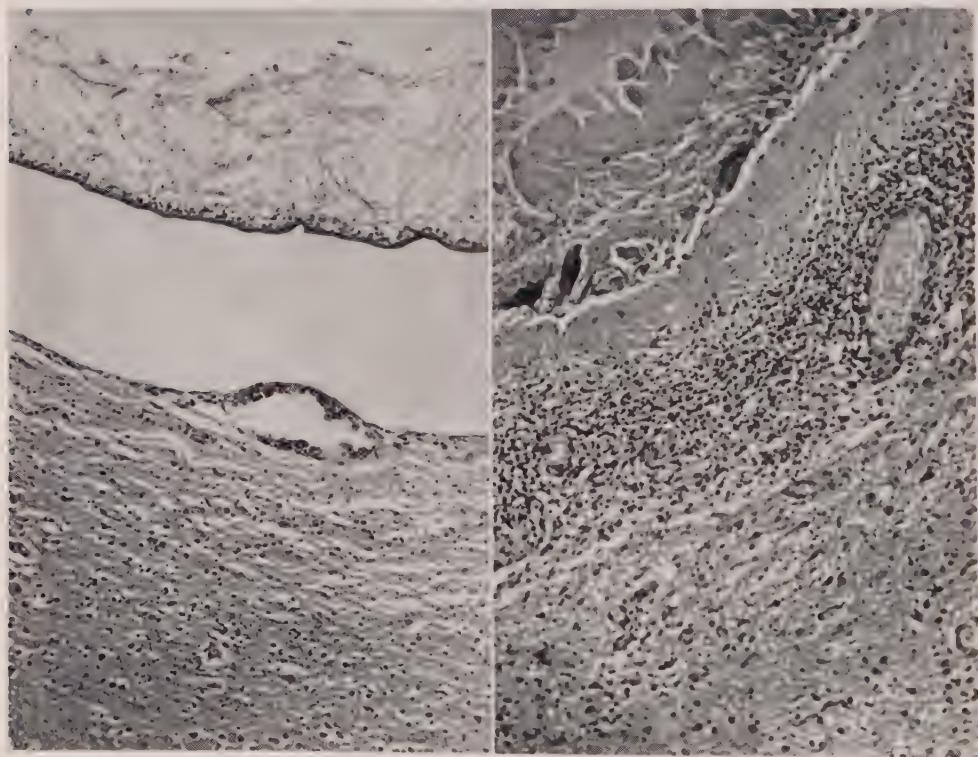


Fig. 282.—Cerebral cysticercosis. A, Part of wall of larval cyst is included above; as long as the cyst is alive, the cerebral substance, below, shows only compression atrophy. B, When the cyst dies it is transformed into formless debris that evokes a granulomatous inflammatory reaction in the surrounding cerebral tissues. ($\times 80$.)

some glial proliferation takes place about the cysticerci, but the general pattern of reaction on the part of the surrounding cerebral tissue is as described in the preceding paragraph (Fig. 282). The blood vessels in the neighborhood of cysts, and even at a distance, show fibrous thickening of the intima. There may be fibrosis of the leptomeninges at the base of the brain, producing internal hydrocephalus. Minute granulations at times develop on the ependymal lining of the ventricles, and there may be fairly extensive infiltration with round cells about small blood vessels, in the neighboring cerebral tissue and in the choroid.¹⁴⁷ When occurring in grapelike clusters in this organ the parasite is referred to as *cysticercus racemosus*. In life the spinal fluid may be under increased tension, with increased globulin and round cells, and at times with eosinophiles.

In the *subcutaneous tissue* the cysts are palpable as firm, ovoid nodules. In the *eye* only one cyst is generally encountered, situated beneath the retina. The inflammation that it provokes leads to iridocyclitis and occlusion of the pupillary opening.

Wherever situated, most of the reaction on the part of the surrounding tissues begins after the death of the contained larva. It takes about five years for the calcification of the cysts, and this occurs later in the brain than in other parts of the body. Peripheral eosinophilia is noted early in the disease, but is rare after the larvae have become encysted. Subcutaneous cysts may first become palpable after death of the larva, since this provokes an increase of their fluid contents. On the other hand, dead cysticerci may be absorbed, in which case the cyst will no longer be palpable, giving the impression in some cases of cysts appearing and disappearing, and even migrating. Subcutaneous nodules may not appear until a few years after the onset of epilepsy. The epileptic fits may be the result not only of the location of the cyst but also of the absorption of decomposition products of the dead larvae.

Immunity.—There is practically no immunologic response to the parasite. Both the intestinal worm and the larvae in the tissues may live for years in their respective situations.

ECHINOCOCCUS DISEASE OR HYDATID DISEASE

Etiology and Life Cycle.—The adult *Echinococcus granulosus* lives attached to the mucosa of the small intestine of the dog, its definitive host. It measures only 3 to 6 mm. in length, and is composed of a head, a neck, and three proglottids. The *head* or *scolex* is provided with four suckers and about 30 to 36 hooklets in a double row; it narrows down posteriorly to form a *neck*. The first proglottid is relatively short and broad, and its genital organs are immature. The second segment is longer, narrower, and mature, while the terminal gravid segment is the longest and broadest.

The eggs, indistinguishable from those of *Taenia solium* and *T. saginata*, are passed free or in gravid proglottids with the dog's feces. If swallowed by intermediate hosts, such as

cattle, sheep, hogs, or man, the oncosphere that is liberated in the duodenum penetrates the duodenal wall and enters venules. The embryos are 30 to 40 microns in diameter. Most of them are filtered out in the liver, but some reach the lungs with the blood, while a lesser number may pass through the pulmonary circulation to the left side of the heart and thus, with the arterial blood, to any organ and tissue. Many of these succumb to the body defenses, while the surviving ones develop into hydatid cysts. The latter contain countless scolices provided with hooklets which represent the future head of the adult tapeworm, and are the larval phase of the parasite. The life cycle is completed when a dog (also wolves, coyotes, and jackals) ingests a hydatid cyst containing scolices on eating the viscera or tissues of the intermediate hosts, mainly sheep.

The cysts are known as *primary* when they develop from the oncosphere or hexacanth embryo, and as *secondary* when produced by the scolices or brood capsules contained in a primary cyst. They are of three different types, according to their structure: the unilocular, the bone hydatid and the alveolar.

The most frequent type in man is the *unilocular* (Fig. 283). If the embryo detained in an organ is not destroyed by the host's reactions, fluid accumulates in its center, a minute vesicle or cyst being formed that is lined by cells that extend from the embryo. Experimentally, a tiny vesicle becomes visible grossly three weeks after infection, and this enlarges to a diameter of 1 cm. at the end of five months. The wall of a fully developed unilocular cyst is composed of three layers: (1) the inner *germinative* or *embryonic membrane*, visible microscopically only, and which rests on (2) a white, soft, *cuticular* or *laminated layer* that possesses no nuclei and is easily separable from (3) the outermost, dense and fibrous *adventitious layer* or capsule developing from the host's tissues.

The limpid and watery fluid that accumulates within these cysts serves for the nutrition and mechanical protection of the scolices. The latter begin to develop when the cyst reaches maturity, some five or six months after infection. First there appear minute heaps of cells in the germinative layer, projecting into the cavity of the hydatid. By central vesiculation of these groups of cells tiny cysts are formed, the *brood capsules* (Fig. 284), that measure up to 1.5 mm. in diameter, and that are attached to the germinative membrane by a delicate pedicle. The scolices develop from the inner aspect of the brood capsules by localized cell multiplication, later with invagination, so that the minute head with its hooklets comes to lie within a cuplike depression. The scolices average 160 by 120 microns and project into the cavity of the brood capsule. Many of the brood capsules and scolices become detached into the hydatid fluid, constituting a fine sediment called *hydatid sand*. *Daughter cysts* composed of an inner germinative membrane and an outer cuticular layer are frequent constituents of hydatid cysts, but they rarely produce scolices.

Hydatid cysts in bones constitute a second type. They usually grow at the epiphyseal end.

Their structure is peculiar in that an adventitia does not develop in osseous tissue. The other layers insinuate themselves between the bony trabeculae, forming multiple diverticula that give the cyst a very irregular outline. The bone undergoes pressure atrophy, ultimately becoming soft and necrotic, so that spontaneous fractures frequently occur. When extension takes place to the medullary canal, the hydatid becomes frankly cystic.

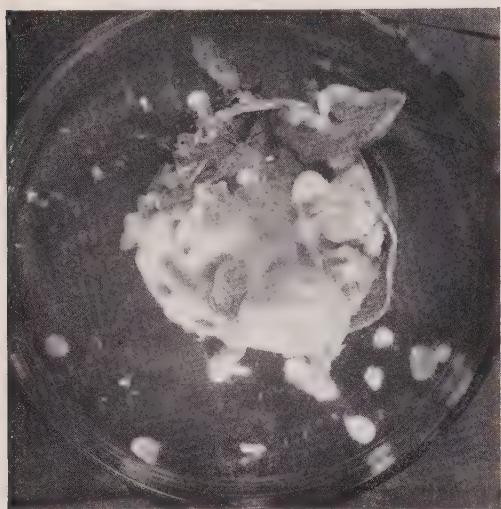


Fig. 283.—Unilocular hydatid cyst, about 2.5 cm. in diameter, opened to show daughter cysts. (From Culbertson: Medical Parasitology, Columbia University Press.)

The third type of cyst is the *alveolar*, which is seen mostly in southern Germany, Switzerland, parts of Russia and Siberia, and only rarely elsewhere. This forms a spongy mass in the liver, composed of an atypical growth of embryonic tissue without the formation of a laminated layer or adventitia, so that microscopic cavities and small cysts pervade the hepatic parenchyma unrestrainedly, rarely extending to other organs by way of blood vessels.

Epidemiology.—Echinococcosis is cosmopolitan in distribution. It occurs mostly in sheep-raising countries like Iceland, Australia, New Zealand, Uruguay, and Argentina. Human cases are also relatively frequent in southern Europe, Switzerland, southern Germany, Austria, parts of Russia and Siberia, Algiers, the Balkans, Arabia, northern China, Japan, and the Philippines. There have been a few autochthonous cases in the United States.

The dog becomes infected by ingesting scolices, the larval form, with the flesh or viscera of intermediate hosts, usually sheep or cattle. The latter acquire the infection by swallowing, with grass or water, ova that are passed with the dog's excreta. Man may become infected by eating vegetables or drinking water contaminated with ova but, more frequently, the eggs are conveyed to the mouth with hands soiled by intimate contact with dogs, especially on the part of children.

The infection is usually contracted in childhood, but because of the slow growth of the cysts clinical manifestations appear more frequently between 20 and 40 years of age.

Pathogenesis and Pathologic Anatomy.—Upon arrival in an organ the embryo instigates a lymphocytic infiltration and histiocytic proliferation about itself. Eosinophiles soon appear, a few giant cells may develop, and hemorrhage may take place; the reaction can be so intense as to destroy the growing embryo. A small cavity lined by the embryo's cells is visible at the end of the second week. By the third week the tiny cyst presents a thin inner lining of flat cells and a narrow laminated layer. The latter is surrounded by a zone of histiocytic proliferation, usually with the cells radially disposed, and of infiltration with eosinophiles and lymphocytes. Peripheral fibrosis begins at about this time. After five months the laminated layer is well-developed, while the zone of histiocytic or epithelioid cell reaction is replaced by the fibrous capsule or adventitia. The surrounding tissues become compressed as the cyst enlarges from the increasing accumulation of hydatid fluid. In the fully developed cyst the laminated layer may be easily separated from the fibrous adventitia, for these layers, although in close apposition, are not fused. The laminated layer is soft, white, and 2 or 3 mm. thick. Microscopically it is composed of very thin, pink, and hyaline strands without nuclei. The germinative layer, 10 to 25 microns thick, has its cells irregularly arranged, or compressed into a single or double row; in fixed tissues it frequently becomes detached from the laminated layer.



Fig. 284.—Hydatid disease. Brood capsule containing scolices, in one of which the hooklets are visible. ($\times 180$.)

Approximately 70 per cent of hydatid cysts develop in the liver and 10 to 15 per cent in the lungs, while the remainder are fairly evenly distributed in the other viscera and tissues. However, the proportion of cysts in the brain is higher in children than in adults.¹⁶¹

Usually, not over 5 or 6 cysts develop in man, but heavy infections with up to 60 primary cysts have been recorded. Except when situated superficially, or in the brain, it generally takes more than five years for signs and symptoms to be produced. The cysts may reach a diameter of 20 cm. Most of the cysts developing in the lungs and brain are unilocular, while in other situations, in adults, they usually produce daughter cysts. After a time the mother cyst collapses, which frequently results in marked fibrosis and calcification of the adventitia. When this occurs in older cysts, the inner portions of the adventitia undergo coagulation necrosis, followed by degeneration of the daughter cysts from impairment of their nutrition. In dead cysts the inner portions become soft and pultaceous.

The *alveolar hydatid* is a tumorlike mass of the liver composed of minute cavities and small cysts embedded in fibrous tissue and containing gelatinous material. The cavities are lined by enlarged cells from the germinative membrane of the embryo, which extend in all directions as naked protoplasmic masses. The laminated layer and adventitia for the most part fail to develop, so that the cystic cavities extend peripherally unchecked, as in a malignant growth. The host's tissues respond to the presence of the embryonic parasitic tissue with histiocytic proliferation, formation of giant cells, and infiltration with eosinophiles, lymphocytes, and plasma cells. Proliferation of the intima of blood vessels leads to narrowing and occlusion of the lumen, which often results in massive coagulation necrosis of the center of the affected portions. Blood vessels and lymphatics may be invaded, with metastasis to other organs. Scolices develop rarely, if ever, in this type of hydatid. The main clinical features of the alveolar hydatid are anorexia, disturbances of digestion, jaundice, hepatomegaly, fever, and a prolonged course. The condition is almost exclusively found in countries where cattle, rather than sheep, serve as intermediate hosts of the parasitosis.

Complications.—These are of frequent occurrence, and comprise mainly the following events: rupture of a cyst into an adjacent viscus, blood vessel, bronchus, duct, or serous cavity; aseptic degeneration of cysts; bacterial invasion with suppuration; entry of bile into a hepatic cyst, and anaphylactic reactions.

Rupture of a hydatid, no matter where situated, may provoke an anaphylactic reaction. The principal allergic and anaphylactic reactions that may develop in the course of this disease are urticaria, fever, dyspnea, vomiting, delirium, and syncope.

Immunity.—It is not known if man develops a resistance to reinfection. The low incidence of the disease after the fourth decade may be indicative of age resistance, but it might also be the result of diminished opportunities for infection after childhood.

Precipitin and complement fixation reactions may be obtainable with hydatid fluid among the infected. With hydatid fluid,^{156, 157} and with antigen prepared from larval forms of other taeniae,^{159, 160} Casoni's intradermal reaction may be applied to advantage for diagnosis.

DIPHYLLOBOTRIASIS

Diphyllobothrium latum, the broad fish tapeworm, is grayish and measures 3 to 10 meters in length. The spatulate scolex, 2.5 cm. long and 1 mm. thick, has two lateral longitudinal grooves or *bothria*, and is continued posteriorly as a thinner, unsegmented neck. The body is composed of 3,000, or more, proglottides. The eggs are broad, ovoid, and operculate; they average 70 by 45 microns.

Man and many other mammals acquire the infection by eating undercooked fish and caviar. The infection occurs in Central Europe, the Baltic States, Roumania, Russia, and parts of the Far East. In the United States it is found in northern Michigan, Wisconsin, and Minnesota. The infection is of no practical importance in the tropics.

The habitat in man is the small intestine. Multiple infections are frequent. In some individuals no symptoms arise, while in others there is asthenia and abdominal pain. An anemia of pernicious type, and with the same anatomic findings at autopsy, has been described in a small proportion of cases of diphyllobothriasis. It seems that the infection acts only as a precipitating factor in the development of the anemia.¹⁶²

Diseases Due to Nematodes

ASCARIASIS

Ascaris lumbricoides is widely distributed throughout the world, ascariasis probably being the commonest helminthiasis affecting man. The adults are cylindroidal, taper toward each end, especially anteriorly, and have a pinkish or pinkish-yellow color. Males measure 15 to 31 cm. in length by 0.2 to 0.4 cm. in diameter, and have the posterior end curved ventrally; females are 20 to 35 cm. long and 0.3 to 0.6 cm. broad. Enormous numbers of eggs are produced daily by each female worm. These are broad, ovoidal, yellow or brown, and covered by a mammillated layer of albumin; they measure 45 to 75 microns in length by 35 to 50 in breadth. The eggs undergo a period of incubation in the soil, the infection being acquired by swallowing the fully embryonated ones, out of which the larva is hatched in the small intestine. The larvae penetrate the wall, reaching the lungs by way of venules or lymphatics. From the alveolar capillaries they pass into the acini, up the respiratory passages, and down with the swallowed saliva, growing into adults of both sexes in the small intestine. In heavy infections some of the larvae continue with the blood from the pulmonary to the general circulation, and so may reach various organs and tissues. Ova begin to appear in the feces from 60 to 75 days after exposure.

During the period of migration of the larvae their passage into pulmonary alveoli produces hemorrhage and infiltration with neutrophiles and eosinophiles, this amounting in heavy infections to a true *Ascaris* pneumonia. Larvae may appear in the sputum at this time, and hemoptysis has been recorded. In experimental human ascariasis the pulmonary manifestations appear from the first to the fifth day after infection.

The mere presence of the adult worms in the small intestine, when not in large numbers, usually is asymptomatic. Worms are expelled spontaneously at defecation, or are vomited from time to time. In the absence of reinfection the parasitism disappears spontaneously within a year, usually without causing serious inconvenience.



Fig. 285.—Adult *Ascaris* worm within acutely inflamed appendix. (Specimen obtained by Dr. David Rodríguez, Municipal Hospital of San Juan, P. R.)

Graver damage is inflicted in some cases, particularly in heavy infections or in repeated ones. The worms have a tendency to wander into natural passages that communicate with the intestines. Thus, they may go up the stomach and esophagus, appearing at the mouth or nostrils, or pass into the larynx and trachea. When present in large numbers they may form knotted masses in the lumen of the small intestine, palpable through the thin abdominal wall of children; intestinal obstruction may supervene in these cases. They may perforate an ulcer in the small or large intestine, pass into the peritoneal cavity, and cause peritonitis.

ENTEROBIASIS OR OXYURIASIS

Etiology and Life Cycle.—*Enterobius vermicularis* is commonly known as the pinworm or threadworm. The female parasite is 8 to 13 mm. long and 0.5 mm. in diameter; it is fusiform, and narrows considerably in its posterior third. The male, one-third as large, is unimportant in pathogenesis. The ova measure approximately 50 microns in length by 25 in breadth, have a doubly contoured shell, and are flattened on one side. They are readily found in swabbings of perianal skin and, much less frequently, in the feces.

The infection is acquired by swallowing the eggs, which are the infective stage, since when discharged by the female they are fully embryonated and need only a few hours to mature. The larvae are hatched in the duodenum, pass downward, while they molt twice and mature, finally reaching the regular habitat of the adult worms, which is the cecum, and to a lesser ex-

tent, adjacent portions of the ascending colon and ileum, and the appendix. They attach themselves to the mucosa by their anterior end. It takes about two months from ingestion of ova to maturation of the worms. The males die after copulation, while the gravid females wander down to the anus when the uterus becomes distended with ova, and come out to crawl over the perianal and perineal regions, where they deposit their ova and die. The wandering about the anus produces itching, and the fingers become soiled by scratching, or by touching clothing or bedclothes contaminated with ova, so that reinfection is maintained by way of the mouth.

Epidemiology.—Enterobiasis is a very common parasitosis of cosmopolitan distribution. Its incidence is highest where personal hygiene is poorest, and since its transmission requires very close contact with the body of the infected, or with their clothing, the condition is more frequent in isolated houses and in institutions, such as schools and asylums. In one series of 2,000 members of the general population the incidence was 51 per cent in children of school age, 35 per cent in those of preschool age, and 22 per cent among adults.¹⁶⁶ In certain institutions and households practically all persons are infected. The ova are very resistant. They have been found suspended with the dust in infested houses, so that air-borne transmission is possible.¹⁶⁸

Pathogenesis and Pathologic Anatomy.—The medical importance of this parasitosis lies mostly in the disturbances produced by the intense *pruritus ani*, particularly in children, in whom it is conducive to restlessness, disturbance of sleep, and, at times, masturbation. Furthermore, the scratching often results in secondary infection.

Organic lesions are rare and unimportant. Considerable interest has centered about the role possibly played by the parasite in the production of symptoms of appendicitis, particularly among children. In a number of cases with the clinical picture of acute appendicitis, the parasite has been found in the appendix in the absence of the usual histologic evidences of inflammation. The term "appendicopathia oxyurica" has been applied to this condition.¹⁶⁵ Although the matter cannot be considered as settled, it is probable that irritation of the mucosa by worms affixed to it may result in appendicular symptoms in some cases. Minute foci of necrosis with very slight cellular infiltration and punctate hemorrhages about the worms may be observed at times.¹⁶⁸ While it is generally believed that any worms found in the submucosa or lymphoid follicles must have arrived there by postoperative or postmortem wandering, Pensö¹⁷⁰ reports penetration and oviposition in the wall, which he interprets as another means of continued reinfection, and as part of the life cycle of the parasite. (See Plate VI, page 760.)

STRONGYLOIDIASES OR STRONGYLOIDOSIS

Strongyloides stercoralis has two developmental cycles. From the ova that are laid in the mucosa of the small intestine of man, *rhab-*

ditoid larvae measuring 200 to 300 microns in length, by 14 to 16 microns in breadth, are hatched and pass out with the excreta. The *direct cycle* is the more common, and consists of a free-living, nonparasitic generation in the soil. The rhabditoid larvae feed on organic matter, growing rapidly into adults (females are 1 mm. long by 50 microns in thickness, and males 0.7 mm. by 36 microns). These copulate, females lay their ova in the soil, and from the latter more rhabditoid larvae are hatched, which grow into free-living adults. Many generations may thus be produced. The *indirect cycle* starts when, under unfavorable conditions, the rhabditoid larvae metamorphose into *filiform*

females average 2.2 mm. in length and 30 to 75 microns in breadth. Parasitic males are like the free-living, and do not invade the wall of the intestine. *Strongyloidiasis* is similar to *ancylostomiasis* in geographic distribution, but it also occurs in more northerly latitudes. As a rule, however, it is less frequent than *ancylostomiasis*, *ascariasis*, and *trichuriasis*.

Under conditions as yet unknown, the rhabditiform larvae, on their way down the intestine, may become infective by *métamorphosing* into *filiform* larvae. These then penetrate the wall of the colon, enter venules, and are taken to the lungs, whence they travel to the small intestine by way of the upper respiratory and alimentary tracts.

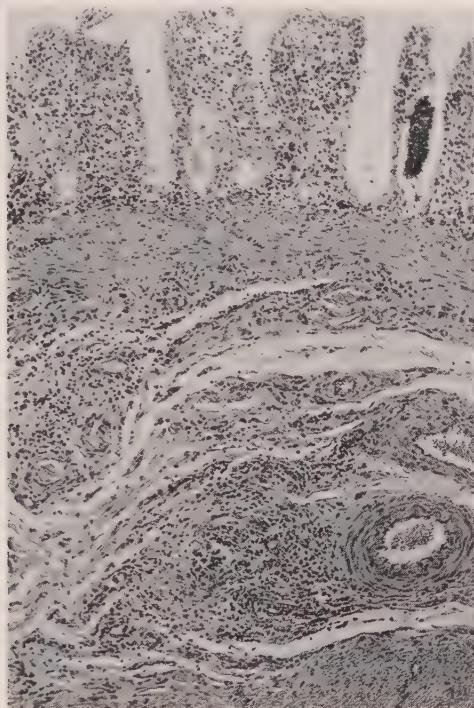


Fig. 286.

Fig. 286.—*Strongyloidal hyperinfection*. The colon presents multiple foci of infiltration with round cells about filariform larvae that invade from the lumen. ($\times 80$.)

Fig. 287.—Detail of Fig. 286. Filariform larva in center, surrounded by lymphocytes, plasma cells, and eosinophiles; there is some proliferation of histiocytes. ($\times 360$.)

larvae, which are about 400 microns in length and 16 in breadth, and represent the mature larval stage infective to man. The *filiform* larvae penetrate through the skin or buccal mucosa, and by entering venules reach the lungs, where they pass from the alveolar capillaries to the acini, as they grow into adolescent worms. They reach the small intestine by going up the bronchi to the larynx and pharynx, being then swallowed. Females may be fertilized in the intestine or at any point after leaving the pulmonary acini. Upon reaching the duodenum or upper parts of the jejunum the females penetrate the mucosa, where they mature and deposit their ova. The parasitic generation may maintain itself in the human host for several years. The parasitic

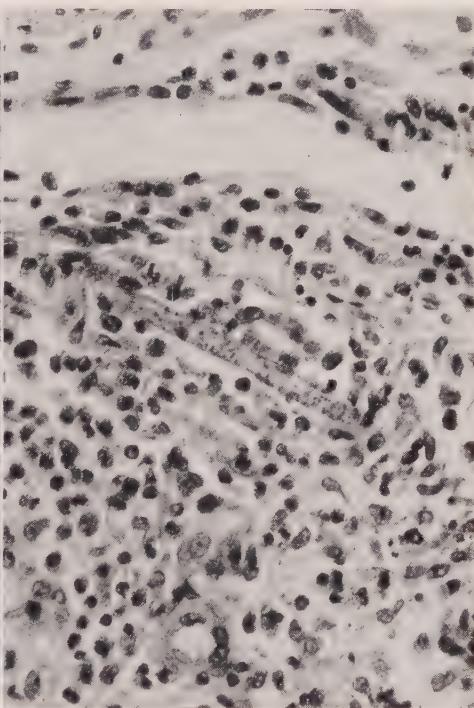


Fig. 287.

This has been called *hyperinfection*. In hyperinfections the gross appearance of the colon, mostly in the distal parts of the sigmoid and rectum, are those of an acute colitis, with reddening of the mucosa and swelling of the submucosa. Microscopic groups of eosinophiles and histiocytes are found about the penetrating filariform larvae in all coats, particularly in the mucosa and submucosa (Figs. 286 and 287).

ANCYLOSTOMIASIS, UNCIARIASIS, OR HOOKWORM DISEASE

Etiology and Life Cycle.—*Ancylostoma duodenale*, the Old World hookworm, and *Necator americanus*, the New World species, are the

cause of intestinal parasitism characterized by secondary anemia, while *Ancylostoma braziliense* is responsible for a purely cutaneous condition known as "creeping eruption."

A. duodenale is white, cylindroidal, and bears teeth in the buccal capsule. The male measures 8 to 11 m. in length by 0.5 mm. in greatest diameter, while the female is 10 to 13 by 0.6 mm. *N. americanus* is grayish-yellow and cylindroidal. It differs from the preceding in being shorter (males measure 7 to 9 mm. in length by 0.3 mm. in greatest diameter; females, 9 to 11 mm. by 0.4 mm.), in bearing cutting plates, instead of teeth, in the buccal capsule, and in having its anterior end so strongly reflexed dorsad as to have suggested the name of hookworm. Males of *A. braziliense* are about 8 mm. long by 0.35 mm. in largest diameter, while the females are 9 to 10 by about 0.4 mm.

The life cycle is similar for the three species, except that *A. braziliense* generally remains in the epidermis, where it dies after a time, and only rarely reaches the intestine. Ova are passed with the feces, and from them *rhabditiform larvae* about 0.25 mm. long are hatched in the soil. By the fifth to the eighth day these have molted and grown into the infective *filariiform larvae* (0.5 to 0.6 mm. long). The latter penetrate through the epidermis, enter venules, and thus reach the lungs, where they pass into the alveoli, and up the air passages to the pharynx. They are then swallowed and so reach the small intestine. There they grow, differentiate sexually, and attach themselves to the mucosa of the small intestine, mostly in the jejunum, through the strongly developed buccal capsules.

Epidemiology.—Hookworm infection is most widely disseminated throughout the warm, moist regions of the tropics and subtropics, but also occurs in temperate lands. *A. duodenale* is found mainly in southern Europe (also more northerly, in mining regions), northern parts of Africa, India, and China, and in Japan, in which regions it is the sole or dominant species. With *N. americanus*, but to a lesser extent, it is also found in Burma, Malaya, Dutch East Indies, the Philippines, Polynesia, Australia, and in limited parts of Paraguay and Brazil. It is occasionally found in other parts of the New World. *N. americanus* is the dominant species in the southern United States, Central and South America, West Indies, Central Africa, southern China down to the Malay Peninsula, southern India, Malaya, Dutch East Indies, Polynesia, and Micronesia. *A. braziliense* is very similar to *N. americanus* in distribution, except for being much more restricted in the Far East and in the Pacific.

Shaded, warm, moist soils rich in decaying vegetation, and not too compact, are ideal for the hatching of hookworm ova, growth of the larvae, and conservation of the infective filariiform ones. Man is the sole reservoir for *A. duodenale* and *N. americanus*; cats and dogs, for *A. braziliense*.

Hookworm anemia is most frequently seen under conditions of poor hygiene caused by poverty and backwardness. Its dissemination requires pollution of soil with infested human excreta, and a barefoot population. Its greatest

incidence extends from childhood to the most productive period of life, the second and third decades, wherein lies its great economic importance, since most of the working members of the population in vast regions are considerably disabled by the anemia. In southern United States *A. braziliense* infestation is usually contracted on beaches or by plumbers working underneath summer cottages.

Pathogenesis and Pathologic Anatomy.—In their passage through the skin the hookworm larvae produce a dermatitis (ground itch), generally in the feet, between and beneath the toes, lasting about two weeks, and characterized by much itching and by an erythematous eruption that later turns papulovesicular. Secondary infection is very frequent, and leads to pustulation and ulceration for several additional weeks.

While passing through the lungs petechial hemorrhages and foci of bronchopneumonia are produced in experimental animals. Similar alterations probably occur in man.

The most important feature of the disease, however, is the production of a secondary anemia, hypochromic and microcytic in type. When coupled, as it frequently is, with deficient nutrition, particularly in animal proteins and iron, and with repeated reinfections, the hemoglobin and red cell values reach very low figures.

The postmortem findings are mainly those of anemia, with marked pallor of all tissues and organs, subcutaneous edema, often generalized, and effusion of clear watery fluid into the peritoneal, pleural, and pericardial cavities. The bone marrow in adults is red or gray-red, and hyperplastic in the middle third of the femur, contrasting with the pallor of the rest of the body; the hyperplasia is mainly normoblastic, but eosinophilic myelocytes may be very numerous. In some severe cases, the marrow has been found to be fatty and inactive.¹⁸² A part, at least, of the edema and serous effusions is probably accounted for by hypoproteinemia. The heart, in advanced cases, is flabby, dilated, and tigered from fatty change. This, together with the anemia, is responsible for much of the final incapacitation of the individual, and for some of the edema and serous effusions. Large numbers of hookworms cling to the mucosa of the small intestine, mostly in the jejunum. In some cases they produce punctate mucosal hemorrhages, or larger hemorrhagic zones that measure as much as 1 or 2 cm. in diameter. The older hemorrhages are of a brown or gray color. The hookworms suck up a minute portion of the mucosa and submucosa into their buccal cavity, and live on the blood and juices that they thus absorb. Extraction of blood by the parasites, oozing from the points of attachment when the worms move to other parts, and malnutrition acting mainly through iron deficiency, are the cause of the anemia. At the point of attachment, infiltration with eosinophiles and lymphocytes, and occasionally hemorrhages, are observed.

In *A. braziliense* infestations the larvae travel along tunnels that they bore between the stratum granulosum and the derma at a variable rate of up to 2.5 cm. daily. At the point of entrance a red papule is formed. The line of advance appears as a serpiginous red streak that becomes

elevated and even vesicular as edema, congestion, and infiltration with round cells and eosinophiles develop about the tunnel. The eruption is itchy, and thus often leads to secondary infection from scratching. "Creeping eruption" usually lasts for one or two months.^{181, 185}

BANCROFTIAN FILARIASIS

Etiology and Life Cycle.—The adult worms of *Wuchereria (Filaria) bancrofti* are white and threadlike. Males are 25 to 40 mm. long by 0.1 mm. in diameter, while females measure 80 to 100 mm. by 0.2 to 0.3 mm. The latter possess a double uterus extending most of the length of the parasite. Thin-walled, ovoid eggs form in the uterus after copulation. The contained embryo elongates into a microfilaria within the delicate eggshell, which is retained as a sheath. Microfilariae in the blood or lymph range from 127 to 320 microns in length and from 7.5 to 10 microns in diameter, and contain minute nuclei arranged in a central column. They do not appear in the peripheral blood of the infected until a year or longer after exposure.

When taken up with the blood of man by mosquitoes of the genera *Culex*, *Aëdes*, *Mansonia*, and *Anopheles*, the microfilariae discard the sheath and penetrate through the wall of the midgut to reach the thoracic muscles. After 10 to 14 days, and through two ecdises, the larvae, which measure about 2 mm. in length by 20 microns in diameter, have moved to the mouth parts of the mosquito, and are mature for transmission to man. When the mosquito bites man, the larvae move down the proboscis, leave it through the tip, and penetrate the skin of the victim; it has not yet been definitely demonstrated whether they enter through the bite puncture or the adjacent skin. It is presumed that, once in the derma, they enter lymphatics, up which they ascend with the lymph to the regional lymph nodes, and that maturity is attained within the larger lymphatic vessels in the neighborhood of the nodes, or within the nodes themselves. Copulation results in the production of large numbers of microfilariae by each female worm. It is thought that, on leaving the parent worm, the microfilariae wander through the neighboring tissues and pass into the lumina of other lymph vessels, ultimately reaching the blood stream by way of the thoracic duct. The life cycle of the parasite is completed when the circulating microfilariae are taken up by a mosquito of suitable species on biting. *Culex quinquefasciatus (fatigans)*, *Aëdes aegypti*, *A. pseudoscutellaris*, and *Anopheles albimanus* are some of the more important vectors.

In most of the endemic foci, with the exception of islands in the South Pacific, the microfilariae are most numerous in the peripheral blood toward midnight (10 P.M. to 2 A.M.), while they are totally absent, or very scarce, during daytime. Since the *microfilarial periodicity* is nocturnal where the vector is night-biting, while microfilariae circulate in the blood both day and night where the mosquito feeds during the day or at dusk, the phenomenon may be an adaptation to the feeding habits of the vector. The mechanism of its production, however, is still unsolved.

Epidemiology.—In Europe bancroftian filariasis is limited to Hungary and Turkey. In

Africa it occurs in the Mediterranean littoral and in extensive areas of the central and western parts of the continent, as well as in Madagascar, Reunion, and Mauritius. In the Middle East it is found along the coast of Arabia, and, in the Far East, in India, Malaya, south China, Korea, and southern Japan. It occurs in northern and northeastern Australia. A great many of the Pacific islands are heavily infected. In the western hemisphere it constitutes an important endemic disease in the Antilles, Panama, Colombia, Venezuela, and Brazil, mostly along the coast, and extends as far south as northern Argentina. There was a small focus in the United States (Charleston, S. C.) until recently, but it appears to have undergone extinction.

Bancroftian filariasis follows malaria and onciariasis in frequency in tropical countries. Its importance lies in the resultant invalidism and in the anxiety provoked by some of its deforming manifestations, particularly when the external genitalia are involved. The disease, of itself, is only rarely the cause of death.

Man is the only known reservoir. The conditions necessary for its propagation are the presence of human beings with microfilariae in the circulation, and a topography and climate suitable to the breeding of the vectors. Low-lying, warm and humid, coastal and riverside areas are ideal, and in many such regions the rate of human infection may be very high. Repeated infections must be common in those places. It seems that for the development of the advanced phases of the disease, more than a few worms must be present in the human host and that, for this to happen in large numbers of individuals, two main factors must concur: (a) a hyperendemic rate with 30 per cent or more of infections among the native population and (b) close and prolonged contact between the prospective victim and the source of infection, since the usual vectors are domestic in their habits and remain within a short radius of human habitations.¹⁹¹

Filariasis is more frequent in males than in females, and in adults after 20 years of age.

Pathogenesis and Pathologic Anatomy.—The habitat of the adult worms is the larger lymphatic channels and the sinuses of lymph nodes. The lymph vessels more commonly involved are those of the extremities, retroperitoneal tissues, spermatic cord, epididymis, and mammary gland. The lymph nodes more frequently affected are the popliteal, inguinal, femoral, epitrochlear, and axillary. The author has seen a well-preserved gravid worm in lymphatics of the gall bladder in one case, and of the parietal pericardium in another.

In the tissues, the microfilariae are usually encountered in the neighborhood of female worms, both in the lumen and wall of the affected lymph vessel, and in the surrounding connective tissue. Less frequently, they may be seen in visceral capillaries (Fig. 288), particularly in the lungs, kidneys, spleen, and liver. Although microfilariae usually produce no visible damage, occasionally they may be found surrounded by a narrow eosinophilic fringe, probably indicative of an antigen-antibody reaction. In a few cases¹⁹⁰ they have been discovered

Fig. 288.

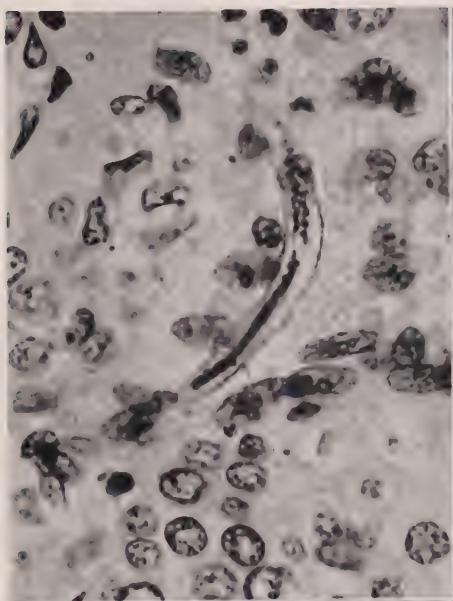


Fig. 289.



Fig. 290.



Fig. 291.



Fig. 288.—Microfilaria of *Wuchereria bancrofti* in thyroid gland removed for unrelated condition. ($\times 776$.)

Fig. 289.—Bancroftian filariasis. Living worms coiled in a dilated afferent lymphatic of a markedly fibrosed inguinal node, and provoking but scant inflammatory reaction in the wall of the lymph vessel. ($\times 80$.)

Fig. 290.—Filarial funiculitis. Eosinophilic pseudoabscess and granulomatous reaction about dead filarial worm, with obliteration of lymphatic vessel. ($\times 80$.)

Fig. 291.—Filarial funiculitis. The smaller lymph vessels about obstructed lymphatics show hypertrophy of walls and obliterative endolymphangitis. The surrounding tissues are densely infiltrated with round cells and eosinophiles. ($\times 80$.)

in the spleen in multiple, firm, red nodules that measure 0.2 to 2.5 cm. in diameter. These are zones of granulomatous reaction of the pulp, showing proliferation of reticulo-endothelial cells and fibroblasts, infiltration with eosinophiles and lymphocytes, and formation of giant cells. At times the microfilariae undergo calcification in the tissues.

The main damage in this disease is brought about by the adult worms.²⁰³ Studies of filariasis contracted by American troops in the South Pacific islands during the Second World War disclosed that bacteria play no part in the pathogenesis, at least in the early stages of the disease, and have emphasized the importance of lesions provoked by the parasite itself.^{198, 205, 206} As long as the parasites remain alive, it is most probable that no serious damage is induced. However, the lymph vessels in their vicinity may exhibit polypoid or diffuse endolymphangitis due to lymphocytic and eosinophilic infiltration, and to proliferation of fibroblasts in the intima, but without complete obstruction. There may be some eosinophilic infiltration of the vessel wall and surrounding tissues. The parasitized lymphatics (Fig. 289) usually show some dilatation, and an irregular hypertrophy of the muscle tissue. At times the worm induces the formation of a lymph thrombus.

Death of the worm provokes a granulomatous inflammatory reaction (Fig. 290). A segment of the worm may be found dead while others still are well-preserved. In the case of female parasites, the double uterus, which may contain ova or microfilariae, will be easily identified if autolysis is not too advanced. Compact masses of eosinophiles, that then undergo necrosis and fragmentation, congregate about the dead segments. Such a focus may superficially resemble an abscess, but it contains few polymorphonuclears and no bacteria. Epithelioid cells, at times perpendicularly arranged, form a barrier about the mass of necrotic eosinophiles, and granulation tissue develops from the subintima of the vessel, filling the lumen about the dead worm. Foreign-body giant cells frequently appear about the disintegrating parasite. The wall of the lymphatic swells from edema and eosinophilic infiltration, both of which processes extend for some distance into the surrounding tissues. Large numbers of lymphocytes and plasma cells also appear, being more numerous than the eosinophiles toward the periphery of the zone of reaction. Not all of the lumen is occupied at once by granulation tissue; portions of it remain open for a time, and may contain blood or thrombotic material. After a while the central focus of necrosis and the worm segments become converted into an amorphous pink mass, and the granulation tissue is replaced by fibrous tissue. Ultimately there is complete scarring, with encapsulation of the necrotic worm, which undergoes absorption or calcification, and with obliteration of the lymphatic. Even though the parasite is usually coiled on itself and about another one of the opposite sex, its length is such that the above pathologic changes affect a not inconsiderable part of the lymphatic vessel. When the parasite dies while within sinuses in a lymph node, the response is similar, except that the zone of epithelioid

cells becomes surrounded by fibroblasts, rather than by granulation tissue. Should the worm load be heavy, the amount of damage that follows repeated attacks of lymphangitis provoked by their death may be such as to preclude all possibility of compensation by the development of a collateral lymphatic drainage.

This is the basic lesion in filariasis, and on it depends the course of the disease, according to the number and location of the worms. Behind the obstruction the lymphatics dilate and hypertrophy, and this is followed by two main results: lymphatic varices and edema of soft tissues. If the obstruction is such that the edema becomes chronic, it leads to progressive proliferation of fibrous tissue, with permanent swelling of certain parts of the body (*elephantiasis*), although usually not until after ten or fifteen years of recurring attacks of lymphadenitis and lymphangitis. However, it is not yet entirely clear whether lymphatic obstruction alone suffices to cause advanced elephantiasis.



Fig. 292.—Elephantiasis of left leg in a woman 57 years of age; the process started twenty-five years ago. (Case of Dr. Federico Hernández Morales, San Juan.)

While it takes at least one year for complete maturation of the worms and for the appearance of microfilariae in the peripheral blood, clinical manifestations usually have their onset seven to nine months after the beginning of exposure to the infection. A large number of individuals in endemic foci carry microfilariae in their blood without developing signs of the disease, perhaps because the worm load is small and the situation of the parasites does not compromise important lymphatic channels in the event of their death.

ELEPHANTIASIS.—The term is synonymous with chronic edema. After repeated attacks of lymphadenitis and lymphangitis of a leg, arm, breast, or of the scrotum, the swelling induced by an attack of lymphangitis does not disappear completely but continues to increase slowly, even though the attacks may be reduced in frequency or even cease altogether for long periods. After ten or fifteen years the swelling may have assumed truly colossal and hideous proportions (Fig. 292). The psychological effect is usually severe,

since elephantiasis may develop in various limbs and parts of the body in the same individual. Furthermore, by the time it is well advanced in one part, other filarial lesions may have also progressed. Elephantiasis is highly prevalent in some parts of the world, like Samoa and the Ellice Islands. While not so frequent in other endemic regions, it is the most important manifestation of late filariasis. It seems fairly certain, however, that its development requires exposure to infective mosquitoes over a period of ten or more years. In endemic areas it rarely appears before the age of 15 years.

The actual pathogenetic factors involved in the production of elephantiasis are difficult of demonstration, and various authors offer somewhat different interpretations. The two factors mainly concerned seem to be filarial obstruction of lymphatic channels and regional lymph nodes, on the one hand, and the effect of repeated attacks of bacterial lymphangitis, on the other.

In most cases of lymphatic blockage of long standing, affecting the extremities, as well as in the older instances of filariasis in other parts of the body, no microfilariae can be found in the peripheral blood.

ONCHOCERCIASIS OR ONCHOCERCOSIS

Etiology and Life Cycle.—*Onchocerca volvulus*, first discovered in Africa, was classified with the *Filariidae* by Leuckart in 1893. Shortly after the disease had been encountered in Guatemala in 1915, the New World parasite was named *Onchocerca cæcutiens* on the basis of morphologic and clinical differences that at present are generally considered not to justify such differentiation. The adult worms are white and filiform, the male measuring about 20 to 40 mm. in length by 150 microns in diameter, and the female, very much longer, 35 to 40 cm. by 300 to 400 microns. The microfilariae are unsheathed, and either short (150 to 290 by 5 to 7 microns) or long (295 to 360 by 6 to 9 microns). They travel freely and widely along the derma, but only rarely appear in the blood or internal organs.

The microfilariae that are ingested by certain tiny flies when they bite man, pass to the vector's thoracic muscles and, following two ecdyses, develop into the infective larvae; this requires six or more days. Transmission is by the bite of the female fly, the larvae going down the proboscis into the skin, where they grow into the adult male and female worms.

Epidemiology.—Onchocerciasis occurs in West and Central Africa and, more restrictedly, in Guatemala and southwestern Mexico.

Small flies (buffalo gnats) are the insect vector: *Simulium damnosum* and *S. neavei* in Africa, and *S. metallicum*, *S. ochraceum* and *S. mooseri* in Guatemala and Mexico. The fly attacks man viciously during the daylight hours. It is found along swiftly moving streams shaded by forests or by grass and bush. The disease tends to occur in limited areas, but in some of these all the inhabitants may be affected. While in America the population is exposed to the fly mainly through their occupation in coffee plantations, in Africa the infection is acquired because the inhabitants' regular habits bring them frequently to the stream beds.^{208, 215}

Pathogenesis and Pathologic Anatomy.—Onchocerciasis is characterized by the formation of subcutaneous fibrous nodules. There may be secondary cutaneous alterations, ocular complications culminating in blindness, elephantiasis of legs and scrotum, and hydrocele.

SUBCUTANEOUS NODULES.—In over 95 per cent of African cases the nodules develop in the trunk (along the crest of the ilium, ribs, and intercostal spaces, and near the axillæ) and about the larger articulations of the extremities (hips, knees, elbows, shoulders), but only rarely in the scalp. In America the reverse holds true. However, there are parts of Africa where scalp nodules and blindness are common,²¹⁶ and, in some Guatemalan and Mexican surveys, up to 16 per cent of patients have presented nodules in the trunk and extremities.²¹¹

The nodules average three to four in each patient, but there may be only one or over 150. They may be so small that only careful palpation will disclose their presence. The smallest have a diameter of 2 to 3 mm., and grow slowly to 4 or 5 cm. Soft and smooth at first, they later become firm and nodular. When situated in the scalp they at times erode the skull because of the pressure exerted on the bone.²¹⁴ They are composed of fibrous tissue surrounding groups of adult parasites (Fig. 293) in a proportion of two or more male worms to each female. The larger ones are firm and well delimited, but worms may protrude from the surface. On section they are composed of a pale, very dense, fibrous external zone that surrounds a softer, yellowish, central area in which there are a few small cystic spaces. These spaces represent tortuous channels in which lie the coiled worms, accompanied by coagulated serum or pus. Microscopically, some of the worms are alive and well preserved, while others are dead and undergoing lysis. Females are easily recognized by the ova and embryos they contain. The parasites are surrounded by a zone of histiocytic proliferation, with formation of giant cells of the Langhans and foreign-body types and infiltration with vacuolated macrophages, lymphocytes, and plasma cells (Fig. 294). Polymorphonuclears are frequently present and, at times, eosinophiles. Outside the zone of histiocytic proliferation and cell infiltration there are proliferating fibroblasts forming fibrous tissue that becomes more compact and collagenous toward the periphery of the nodule.

Microfilariae in variable numbers are present in the derma in wide areas of the skin adjacent to the nodules (Fig. 295). In a few cases they have been found in the skin in the absence of detectable nodules. It is not known whether this means that there may be undetectable, deep-seated nodules, or whether adult worms may occasionally be present without leading to their formation. In two autopsies, worms were encountered free in the subcutaneous tissue.²¹⁷ The onchocercal nodules at times become secondarily infected and suppurate. In some Negroes they become keloidal.

CUTANEOUS ALTERATIONS.—The presence of even large numbers of microfilariae in the derma may give rise to no symptoms or pathologic alterations. At times, however, there is marked, chronic pruritus, which has been explained on the basis

of an allergic manifestation to products of the adult worms and not to the embryos.²⁰⁹ The itching may be confined to areas over which the skin thickens after a time and becomes pseudoichthyotic. In some cases, papules appear over the back, buttocks, and external aspects of thighs and arms.²¹⁰ Microscopically, there is thickening of the stratum corneum and some infiltration of the corium with lymphocytes, plasma cells, and eosinophiles. Microfilariae may be absent, particularly in very chronic cases, while in others they are found in variable numbers, more abundantly in the neighborhood of nodules.

OCULAR INVOLVEMENT AND BLINDNESS.—It is the involvement of the eyes and the consequent blindness that makes onchocercosis a disease of importance, for the nodules in themselves are not of serious import, and the filarial infestation does not impair the general health. This complication is found in from 5 to 20 per cent of Guatemalan and Mexican cases, and is the result of invasion of the eyeball by the microfilariae which wander into the organ from onchocercal nodules situated in the head or upper parts of the trunk. Beginning with photophobia and lacrimation, the disease may progress to dimness of vision and ultimate blindness.

First there is a punctate keratitis, with the formation of tiny white opacities in the cornea

near the limbus, at each end of the equatorial meridian, accompanied by circumcorneal injection. The conjunctival blood vessels are surrounded by lymphocytes, plasma cells, large mononuclears, and fewer polymorphonuclears and eosinophiles. The cornea in the affected portions is focally infiltrated with round cells, eosinophiles, and macrophages, and is vascu-

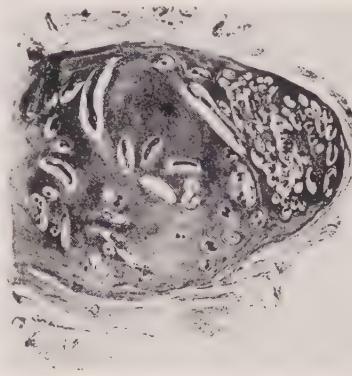


Fig. 293.—Subcutaneous onchocercal nodule showing tunnels within which lie the adult worms. ($\times 15$.) (From Dr. James T. Culbertson, Medical Parasitology. Columbia University Press.)



Fig. 294.

Fig. 294.—Onchocercosis. In the nodules some segments of the worms are surrounded by epithelioid and giant cells, and by numerous round cells and eosinophiles; further away there is dense fibrosis. ($\times 80$.)

Fig. 295.—Onchocercosis. Microfilariae may be found in large numbers in the neighborhood of the subcutaneous nodules and in the derma. ($\times 180$.)

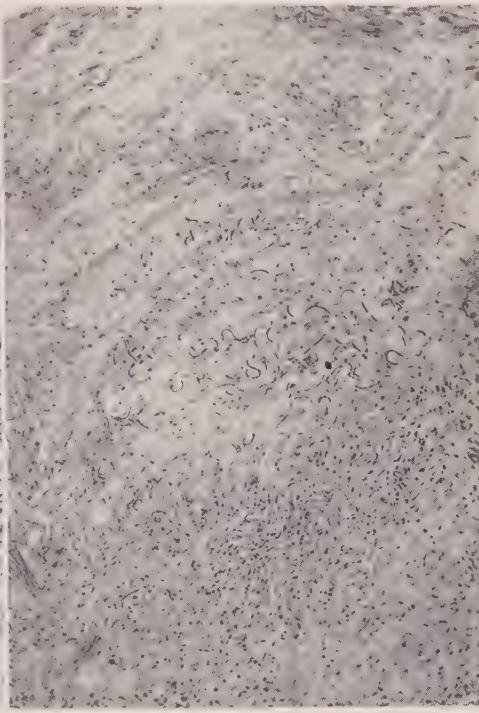


Fig. 295.

larized. Descemet's membrane becomes folded over projections of fibrous tissue. Next, the iris, ciliary body, choroid, and retina become involved. Disturbances of vision have their onset as microfilariae begin to appear in the vitreous. The alterations are chronic inflammatory in nature, mostly with edema and perivascular infiltration with plasma cells and lymphocytes, and later with fibrosis. There may be secondary degenerative changes in the crystalline lens, exudation of fibrin and leukocytes into the anterior chamber, and formation of anterior synechiae. The last brings about fixation of the pupil, and gives it a characteristic triangular shape with the apex pointing downward. There are disturbances in the distribution of pigment in the iris and retina. Lastly, after about five or six years, there may supervene total blindness with glaucoma, phthisis bulbi, and optic neuritis.

The microfilariae are most abundant in the conjunctiva and corneal limbus. They later invade the ciliary body, vitreous, and optic nerve sheath. No inflammatory reaction is excited about them while living, but round cells, polymorphonuclears, and eosinophiles collect about the dead ones.^{207, 212, 215, 216}

LOAIASIS

Loa loa, the "eye worm," is filiform and white. Males measure 30 mm. in length by 0.4 mm. in diameter, and females 50 to 70 mm. by 0.5 mm. The microfilariae are more numerous in the blood in daytime (diurnal periodicity). They bear a sheath, and are 250 to 300 microns long by 6 to 8 in diameter. The geographic distribution is limited to tropical West Africa, particularly in the coastal plains and up the Congo River for a distance of 1,500 miles. Although brought to the Antilles, Brazil, and other parts of the western hemisphere by slaves, the infection never became implanted there, undoubtedly because of the absence of a suitable intermediate host. Tabanid flies (*Chrysops dimidiata* and *C. silacea*) are the intermediate hosts and vectors. The female flies bite during the day. The ingested microfilariae pass through three larval stages in the fatty tissue and thoracic muscles before they can be infective. The disease is transmitted by the bite of these flies. In some of the endemic foci most of the inhabitants are infected.

In this form of filariasis the worms grow in the subcutaneous tissue, through which they travel at the rate of about 1 cm. per minute, producing an annoying creeping sensation and, at times, some itching or pricking. They wander through most parts of the body, and in some situations their serpiginous outline becomes visible externally. They have been found in internal tissues, such as the heart, and may wander through the neck of the bladder, producing much pain. They may enter the anterior chamber of the eye. Not infrequently they appear beneath the ocular conjunctiva, causing congestion, lacrimation, and considerable annoyance.

In the course of this infection there appear, at irregular intervals, the so-called Calabar or fugitive swellings. These develop suddenly in any part of the body, are generally painless, last for two or three days, and disappear slowly. They average 4 or 5 cm. in diameter. At times

they become chronic and cystic. Calabar swellings probably represent an allergic manifestation to some product of the parasite. A high peripheral eosinophilia is usually present in the course of loiasis. Microfilariae may not appear in the blood until three or four years after the individual has left the endemic area, and the adult worms may live for as long as fifteen years.

The worms often undergo calcification, and at times their death provokes the formation of an abscess, from secondary bacterial contamination. A few cases of hydrocele have been recorded. Multiple small fibrotic nodules of the spleen, accompanied by eosinophilic infiltration, and by the presence of microfilariae, have been described in two cases.²¹⁸

DRACUNCULIASIS, DRACUNCULOSIS, OR DRACONTIASIS (GUINEA-WORM INFECTION)

Dracunculus medinensis, the medina or guinea worm, is milky white and cylindroidal. Only one complete male, 40 mm. long, has been recovered from man. Females average 1 meter in length and about 1.5 mm. in thickness. The infection is frequent in parts of the Near East (Persia, Turkestan, Arabia), western India, and Africa (Nile Valley, Uganda, Northwest Coast, West Africa).

The embryos (650 to 750 microns long by 17 microns in diameter) are discharged from the females lying in the subcutaneous tissue of the human host through a small puncture in the skin. This must happen under water for them to be able to enter certain species of freshwater crustaceans (copepods) of the genus *Cyclops*, by which they are avidly hunted and ingested. In ten or twelve days the embryos have matured into larvae 1 mm. long that represent the stage infective to man. When the latter swallows the crustacean, on drinking water, the larvae are liberated by the action of the gastric juice on the intermediate host. The larvae penetrate through the wall of the stomach or small intestine, and seek the connective tissue of various parts of the abdominal cavity, where they mature into adult worms in about twelve months. This part of the cycle is but imperfectly known. The male probably dies soon after copulation and is absorbed, while the gravid female wanders out to the subcutaneous tissues, mostly of the legs and feet.

There are no signs and symptoms of the disease until the worm reaches the subcutaneous tissue and is ready to discharge its content of embryos. A few hours before the worm has been noted in a given area, slight fever and an erythematous or urticarial rash make their appearance. The early manifestations, however, may be more severe, with cyanosis, dyspnea, vomiting, diarrhea, fainting, and even syncope. A small, red and itchy papule then appears, followed within twenty-four hours by the formation of a central blister, beneath which lies the head of the worm. The blister varies in diameter from 2 mm. to 7 cm., the larger ones being those that do not rupture until after three or four days. As a rule the blister opens spontaneously within a day or two after on-

set of the early manifestations. This leaves an ulcer with a base composed of granulation tissue, in the central part of which there is a small necrotic portion that later becomes a tiny opening through which fluid rich in embryos is discharged, especially when the affected part is under water. At times there appears at this opening a milky white thread, which is a segment of the worm's uterus that has extruded out of a break in the parasite's body. The segment fills up with milky fluid and ruptures, discharging enormous numbers of embryos. The process may continue intermittently during several days or weeks, after which the worm dies in situ.

The blister is probably produced by fluid released by the worm when its head comes in contact with the epidermis. This fluid also seems responsible for the first symptoms, all of which appear to be of anaphylactic nature. The blister develops between the basal cell layer and the derma; it contains fluid from the worm, serum, and many eosinophiles, lymphocytes, and plasma cells. Before rupture it is divided horizontally by a delicate fibrinous membrane of gelatinous appearance, beneath which the worm's head may be seen as a tiny milky spot. The parasite lies parallel to the epidermis, within a tortuous tunnel bored in the superficial parts of the subcutaneous tissue. About it there forms a sheath of concentrically arranged fibroblasts, surrounded in turn by a zone of dense infiltration with eosinophiles, lymphocytes, and plasma cells. The tunnel frequently becomes secondarily infected with bacteria that grow in from the ulcer, particularly following attempts at extraction, after which formation of a subcutaneous abscess is a common complication, on which cellulitis may be superimposed, and even septicemia. The worm may die before its head has reached the epidermis, and may undergo calcification with the formation of a long-lasting firm cord.

The worms usually present themselves in the legs, but they may appear in the trunk and arms, more rarely in the buttocks or scrotum, and exceptionally in the scalp, mouth, spinal musculature, and perirenal tissues. Arthritis, epididymitis, contractures of tendons, and ankylosis of joints may result from unusual localizations of female worms, mostly when their death is followed by bacterial infection. At times the guinea-worm ulcer becomes chronic and much indurated. As many as 56 worms have been counted at one time in a patient, but in most cases there are only one or up to three.

TRICHINIASIS, TRICHINOSIS, OR TRICHINELLIASIS

Etiology and Life Cycle.—*Trichinella spiralis* was discovered by Paget in 1835, encysted in human muscle, but its clinical importance was not realized until Zenker's postmortem studies in 1860. The male worm measures 1.6 mm. in length and 50 microns in diameter; the body broadens toward the posterior end. The female is viviparous and 3 to 4 mm. long by 60 microns in breadth. The newborn larvae, as seen in the blood, are cylindrical, and average 100 microns

in length by 6 microns in diameter. Within muscle fibers they grow to a length of 1 mm. and a breadth of 35 microns.

When raw or undercooked pork and its products contain trichina cysts, these are liberated in the stomach during digestion. They pass to the small intestine, where the larvae attach themselves to the mucosa, attaining sexual maturity in one or two days. Copulation takes place within the mucosa, the male dying soon after its accomplishment. The female is fixed to the mucosa by the anterior end, so that most of the larvae pass directly into the tunica propria at birth. Larviposition begins on the seventh day after ingestion of the trichinous meat and continues until the end of the sixth week, by which time each female has produced 1,000 to 1,500 larvae. The female dies at the end of larviposition. While some of the larvae may pass into the intestinal lumen at birth, so being lost, most of them enter lymphatics or venules in the tunica propria. Those entering lymphatics will pass the regional lymph nodes and reach the venous circulation by way of the thoracic duct. After going to the right side of the heart and through the pulmonary circuit, they are carried with the arterial blood to all organs and tissues of the host.

Most of the larvae settle in striated muscles of the voluntary type. On reaching the muscles they leave the capillaries and penetrate individual muscle fibers. Some are lost in various organs, or by passing into the spinal fluid or serous cavities. Once in the muscle fibers they coil in corkscrew fashion and encyst. In this location they are able to survive for years, although some of them begin to perish and to calcify within six months. The larvae that reach cardiae muscle do not encyst but soon disappear.

Epidemiology.—Although this is a cosmopolitan malady, it is most common in the temperate parts of the United States and Europe. It has also been reported from parts of Africa, South America, China, and India. The disease is very frequent in the United States, where the general incidence at autopsy is about 18 per cent. However, most of the cases are asymptomatic, and the mortality is low, there having been a total of only 5,000 to 6,000 deaths reported from the year 1842 to 1937.²²⁶

Man becomes infected by eating raw or partly cooked pork or its products, so that in thorough cooking lies the most effective method of prevention. The hog is infected by eating trichinous pork from uncooked garbage; very probably this is also the source of trichinosis in the wild rat.²²⁷

Pathogenesis and Pathologic Anatomy.—In most cases, trichiniasis runs its course as a sub-clinical infection, or with symptoms so mild and atypical that the true diagnosis is missed. The gravity of the disease depends mostly on the number of larvae reaching the muscles, but the size and age of the patient also play a part. In well-defined cases the disease evolves through three stages. The stage of invasion lasts two to seven days, during which the adult worms are in the intestinal lumen, or attached to the mucosa of the duodenum and upper jejunum in the process of copulation. Symptoms at this

time are those of gastrointestinal irritation, with nausea and vomiting, abdominal discomfort, and diarrhea or constipation. The *stage of migration* extends from the seventh day to the end of the fifth week, during which period the larvae are migrating to their definitive position in the musculature, and to certain organs. Symptoms are very variable at this time, but the more frequent and characteristic are muscular pain, prostration, fever, chemosis of the conjunctivae, edema about the eyes, "splinter hemorrhages" beneath finger- and toenails, and marked eosinophilia. When death occurs, it usually supervenes from the fourth to the sixth week. The *stage of convalescence* corresponds to that of encystment of the larvae and the end of their migration from the intestine.

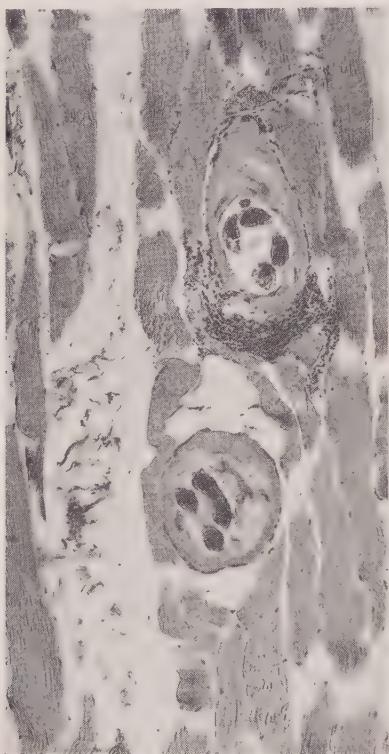


Fig. 296.—Two *Trichina* larvae encysted in voluntary muscle of rat infected experimentally. ($\times 180$.)

Pathologic changes in trichinosis are mainly induced by the larvae, and are found mostly in skeletal and cardiac muscle. In some cases the lungs, brain, and meninges are also involved. Since death rarely occurs before the third week, the damage done by the adult worms to the small intestine during the first week is unknown, but it appears to be unimportant. In experimental animals there is infiltration of the mucosa with lymphocytes, eosinophiles, and some polymorphonuclears, and there may take place hemorrhage into the mucosa, and superficial ulceration.

At autopsy the gross findings are not characteristic. Contracture of the elbows and wasting

are often present. There may be petechial hemorrhages and ecchymoses into the skin and some of the serous membranes, like the epicardium and pleura. The more common gross features are marked congestion of the mucosa and edema of the wall of the small intestine, enlargement and congestion of the mesenteric lymph nodes, congestion, edema, and focal hemorrhages in the lungs, and petechial hemorrhages in the brain.

The muscles more frequently affected are the diaphragmatic, intercostal, extraocular, masseteric, lingual, laryngeal, and cervical. Grossly they are not characteristically altered during the period of larval migration, but they may be darker and firmer than normal, and may present a few small hemorrhages. After the fifth week, tiny gray streaks, up to 2 mm. long, may be visible. The invaded muscle fibers are swollen, basophilic, and without striations. After the eighteenth day shrinkage takes place, while the contained trichina coils up and becomes surrounded by a halo of basophilic material from the muscle fibers. The adjacent muscle fibers undergo hyaline or hydropic degeneration, and their nuclei increase in number. The interstitial connective tissue is edematous, congested, and infiltrated with eosinophiles, polymorphonuclears, lymphocytes, and macrophages for a short distance about the affected muscle fibers. Foreign-body giant cells may occur, particularly when the larva dies before encapsulation. The inflammatory changes are most active from the fifth to the sixth week. A capsule then forms about each trichina, composed of an inner portion of granular basophilic material of the muscle fiber and an outer hyaline, pink part representing the thickened sarcolemma. A small ovoid cyst is thus formed within which, if there has been no marked invasion by leukocytes at the beginning, the trichinæ may be preserved alive for years (Fig. 296). These cysts average 0.4 by 0.26 mm. Their wall begins to calcify six months after infection, and the trichinæ themselves will undergo calcification in old infections. At times the cavity of the cyst may be found either empty or occupied by fat cells or connective tissue.

The *myocardium* usually is soft, and it may be pale. The pericardial fluid may be increased, and larvae are found in it at times. The disease produces a myocarditis that is most marked close to the serosal surfaces. There are foci of necrosis of muscle fibers and of interstitial infiltration with the same cells as in other muscles, eosinophiles often predominating. Hemorrhage into the muscle may take place. The myocarditis is produced by the larvae, but these soon disappear, and are rarely demonstrable in human hearts at autopsy. Encystation does not occur in cardiac muscle.^{223, 230}

The *brain* may be congested and stippled with hemorrhages. Microscopically there is congestion and dilatation of perivascular lymph spaces. In the white matter particularly, but also in the cortex, basal ganglia, cerebellum, pons, medulla, and spinal cord there may appear microscopic nodules of glial cells, lymphocytes and plasma cells about larvae; polymorphonuclears and eosinophiles may also be present. Foci of degeneration of the cerebral substance with neuronophagia and satellitosis, some perivascular infiltration

tion with lymphocytes and plasma cells, and round-celled infiltration of the leptomeninges have also been found in some cases.^{225, 228} In one case larvae were encountered in the retina, where they produced minute foci of edema, infiltration with lymphocytes and polymorphonuclears, and proliferation of endothelial cells of capillaries.²³¹

The lungs may present small foci of hemorrhage produced by the obstruction of alveolar capillaries during the period of migration. However, congestion, edema, bronchitis, and bronchopneumonia are common incidental findings. Additional alterations are hyperplasia of the bone marrow, in which eosinophilic cells are markedly increased, fatty changes of the liver, and cloudy swelling of the kidney. At autopsy the small intestine may show edema of the wall, congestion of the mucosa, and petechial hemorrhages or ecchymoses in the latter coat. The mesenteric lymph nodes, rarely other abdominal or thoracic nodes, may be enlarged, soft, and congested, or with a gray or yellow tinge. The lymph sinuses may contain mobilized littoral cells, eosinophiles, and larvae, but the last are only rarely encountered.

Immunity.—A few cases of reinfection are known, and at least one instance in which a first infection protected against a second one. In experimental animals, a previous attack, even with relatively few trichinae, produces durable resistance to reinfection. Immunity in this disease is expressed in the inability of the adult worms to obtain a hold in the mucosa of the small intestine, so that they are passed with the feces, although not damaged.²²⁷ This appears to be the expression of a general humoral response acting locally on the intestinal mucosa.

Positive complement fixation and precipitin tests, and a cutaneous reaction, are obtainable in trichinosis, the latter two being of valuable aid in diagnosis.

TRICHOCEPHALIASIS OR TRICHURIASIS

Trichocephalus trichiurus or *Trichuris trichiura*, the whipworm, is one of the commonest intestinal parasites of man in the tropics, but its distribution is world-wide. The worm is filiform anteriorly, becoming slightly thicker in its posterior two-fifths. Females are 4 to 5 cm. long. The male, somewhat shorter, has its posterior end coiled on itself ventrally. The eggs, 50 by 22 microns in size, are brown and barrel-shaped, with an albuminous knob at each end. The infection is acquired by swallowing eggs that have matured in the soil, the larva being released in the small intestine. The parasite matures in about one month while attached to the mucosa of the latter, then moving down to its usual habitat which is the cecum. It may also be found in adjacent portions of the ileum and colon, and in the appendix.

The adult worm is very lightly implanted, the anterior tip rarely penetrating below the muscularis mucosae. This provokes practically no reaction on the part of the tissues; at times a slight infiltration with eosinophiles is seen in the mucosa immediately about the parasite. In most cases no symptoms can be attributed to the infection, but some observers believe that it may be responsible for nervousness, anorexia,

and some abdominal discomfort, and even for acute appendicitis. Eosinophilia is often present. In rare cases abdominal pain, diarrhea, severe anemia, subcutaneous edema, and emaciation develop, the picture then being much as in severe uncinariasis. At autopsy these cases have shown cardiac dilatation, and whipworms, in incredible numbers, from the cecum down to the descending colon and even to the rectum, form a grayish mat on the mucosa. The latter may be unaltered, or only congested, or it may present a few uncharacteristic ulcers, not over 1 cm. in diameter.

References

Amebiasis

- Armitage, F. L.: J. Trop. Med. & Hyg. 22: 69, 1919 (amebic abscess of the brain).
- Clark, H. C.: Am. J. Trop. Med. 5: 157, 1925 (distribution of amebic lesions).
- Craig, C. F.: The Etiology, Diagnosis and Treatment of Amebiasis, Baltimore, 1944, Williams & Wilkins.
- Faust, E. C., and Kagy, E. S.: Am. J. Trop. Med. 14: 221, 1934 (pathology of amebic enteritis in dogs).
- Halpert, B., and Ashley, J. D., Jr.: Arch. Path. 33: 112, 1944 (abscess of brain).
- Hegner, R., Johnson, C. M., and Stabler, R. M.: Am. J. Hyg. 15: 394, 1932 (experimental amebiasis).
- James, W. M.: Ann. Trop. Med. & Parasit. 22: 201, 1938.
- Marrison-Baird, P.: Trans. Roy. Soc. Trop. Med. & Hyg. 32: 223, 1938 (amebic invasion of skin).
- Palmer, R. B.: Arch. Path. 25: 327, 1938 (changes in the liver).
- Rogers, L.: Lancet 1: 463, 1922 (amebic liver abscess).
- Stitt, E. R.: Diagnosis, Presentation and Treatment of Tropical Diseases, ed. 7, Philadelphia, 1945, The Blakiston Co.

Trichomoniasis

- Feo, L. G.: Am. J. Trop. Med. 24: 195, 1944.
- Trussell, R. E., and Johnson, G.: Puerto Rico J. Pub. Health & Trop. Med. 20: 289, 1945.

African Trypanosomiasis

- Final Report of the League of Nations International Commission on Human Trypanosomiasis, Geneva, 1928.
- Bertrand, L., Bablet, J., and Sicé, A.: Ann. Inst. Pasteur 54: 91, 1935 (lesions of nervous system).
- Calwell, H. G.: Roy. Soc. Trop. Med. & Hyg. 30: 611, 1937 (lesions of the brain).
- Graf: Arch. f. Schiffs- u. Tropen-Hyg. 33: 219, 1929.
- Hawking, F., and Greenfield, J. G.: Trans. Roy. Soc. Trop. Med. & Hyg. 35: 155, 1941 (visceral lesions).
- Kellersberger, E. R.: Am. J. Trop. Med. 13: 211, 1933.
- Lavier, G., and Leroux, R.: Bull. Soc. path. exot. 32: 927, 1939 (cardiac lesions).
- Le Port, L. R.: Bull. med. du Katanga 12: 41, 43, and 51, 1935.
- Lester, H. M. O.: Ann. Trop. Med. & Parasit. 27: 361, 1933.
- Low, C. L., and Castellani, A.: Rep. Sleep. Sick. Comm. Roy. Soc. No. 5, page 14, 1903 (clinical aspects).
- Mall, A. H.: Liverpool Sch. Trop. Med. Memoir XXI, 1906 (lesions in the lymphatic glands).
- Mott, F. W.: Sleep. Sick. Comm. Roy. Soc. Report VII, 1906 (histologic observations).
- Peruzzi, M.: Final report of the League of Nations International Commission on Human Trypanosomiasis, Geneva, 1928.
- Sicé, A.: Bull. Soc. path. exot. 23: 77, 1930.

28. Taliaferro, W. H.: The Immunology of Parasitic Infections, New York, 1929, The Century Co.
29. Thomas, H. W., and Breinl, A.: Liverpool Sch. Trop. Med. Memoir XVI, 1905 (pathology and treatment).
30. van den Branden, F., and Appelmans, M.: Ann. Soc. Belge de Méd. Trop. 14: 91, 1934.
31. Yorke, W., Adams, A. R. D., and Murgatroyd, F.: Ann. Trop. Med. & Parasit. 24: 115, 1930.

Chagas' Disease

32. Chagas, E.: Compt. rend. Soc. de biol. 116: 1153, 1934.
33. Chagas, E.: Compt. rend. Soc. de biol. 117: 390, 1934.
34. Chagas, E.: Mem. Inst. Oswaldo Cruz 30: 387, 1935.
35. Crowell, B. C.: Am. J. Trop. Med. 3: 425, 1923 (pathology of acute form).
36. De Coursey, E.: Am. J. Trop. Med. 15: 33, 1935.
37. Dias, E.: Mem. Inst. Oswaldo Cruz 28: 1, 1934.
38. Guerreiro, C., and Machado, A.: Brazil-Medico 27: 225, 1913.
39. Johnson, C. M., and de Rivas, G. T.: Am. J. Trop. Med. 16: 47, 1936.
40. Kelser, R. A.: Am. J. Trop. Med. 16: 405, 1936 (complement-fixation test).
41. Kraus, R.: Wien. klin. Wochenschr. 39: 378, 1926.
42. Lundeberg, K. R.: Am. J. Trop. Med. 18: 185, 1938.
43. Malamos, B.: Arch. f. Schiffs- u. Tropen-Hyg. 39: 156, 1935.
44. Mazza, S., and Romaña, C.: Univ. de Buenos Aires, Misión de Estud. de Patol. Reg. Argent. Publ. 15, p. 25, 1934.
45. Mazza, S., Romaña, C., and Parma, B.: Ibid. Publ. 21, p. 3, 1935.
46. Mazza, S., and Benítez, C.: Ibid. Publ. 31, pp. 1-31, 1937.
47. Mazza, S., and Urcelay, G.: Ibid. Publ. 46, pp. 58-84, 1940.
48. Mazza, S., and Salica, P. R.: Ibid. Publ. 54, pp. 3-21, 1941.
49. Mazza, S., Loyaglio, J., and Grondona, B.: Ibid. Publ. 45, pp. 49-85, 1940.
50. Mazza, S.: Ibid. Publ. 51, pp. 3-74, 1941.
51. Mazza, S., Miyara, S., and Jorg, M. E.: Ibid. Publ. 68, 1944.
52. Reichenow, E.: Arch. f. Schiffs- u. Tropen-Hyg. 38: 499, 1934.
53. Romaña, C.: Univ. de Buenos Aires, Misión de Estud. de Patol. Reg. Argent. Publ. 14, pp. 3-24, 1934.
54. Romaña, C.: Semana méd. 42: 897, 1935.
55. Romaña, C.: Univ. de Buenos Aires Misión de Estud. de Patol. Reg. Argent. Publ. 22, pp. 16-28, 1935.
56. Talice, R. V., Costa, R. S., Rial, B., and Osiomani, J. J.: Universidad de Montevideo, Uruguay, A. Montevideo y Cía., editores, 1940.
57. Torres, M.: Mem. Inst. Oswaldo Cruz 9: 114, 1917.
58. Yorke, W.: Trop. Dis. Bull. 34: 275, 1937.

Visceral Leishmaniasis

59. Acton, H. W., and Napier, L. E.: Indian J. M. Research 15: 97, 1927 (dermal leishmaniasis).
60. Chorine, V.: Ann. Inst. Pasteur 58: 78, 1937 (serology).
61. Forkner, C. E., and Zia, L. S.: J. Exper. Med. 59: 491, 1934 (transmission).
62. Hu, C. H.: Chinese M. J., Feb. 1936, Suppl. I, pp. 1-12 (pathologic anatomy).
63. Jemma, R., and Di Cristina, G.: Zentralbl. f. Bakter. 59: 109, 1911.
64. Kirk, R.: Tr. Roy. Soc. Trop. Med. & Hyg. 35: 257, 1942.
65. Meleny, H. E.: Am. J. Path. 1: 147, 1925 (histopathology).
66. Perry, H. M.: J. Roy. Army M. Corps 39: 323, 1922.
67. Sen Gupta, P. C.: Indian M. Gaz. 78: 336, 1943 (complement fixation test).
68. Sun, C. G.: Personal communication.

69. Swaminath, C. S., Shortt, H. E., and Anderson, L. A. P.: Indian J. M. Research 30: 473, 1942 (transmission).

Mucocutaneous Leishmaniasis

70. Castro Ferreira, L., Mangabeira, O., Deane, L., and Chagas, A. W.: Hospital 14: 1077, 1938 (transmission).
71. Costa, O. G.: Arch. Dermat. & Syph. 49: 194, 1944.
72. Delamare, M. G., Gatti, C., and González, D.: Bull. Soc. path. exot. 25: 488, 1932.
73. d'Utra e Silva, O.: Mem. Inst. Oswaldo Cruz 7: 213, 1915.
74. Geiman, Q. M.: Suppl. to J. Parasitol. 26: 22, 1940 (Abst. No. 25).
75. Kligler, I. J.: Tr. Roy. Soc. Trop. Med. & Hyg. 19: 330, 1925-26.
76. Klotz, O., and Lindenberg, H.: Am. J. Trop. Med. 3: 117, 1923 (leishmaniasis of the nose).
77. Laveran, A.: Bull. Soc. path. exot. 8: 284, 1915.
78. Llambias, J., and Mosto, D.: Semana médica 33: 536, 1926 (histologic studies).
79. Marques da Cunha, A.: Brasil-med. 52: 849, 1938.
80. Mayer, M., and Ray, J. C.: Arch. f. Schiffs- u. Tropen-Hyg. 32: 277, 1928.
81. Noguchi, H.: J. Exper. Med. 44: 327, 1926.

Cutaneous Leishmaniasis

82. Adler, S., and Ber, M.: Indian J. M. Research 29: 803, 1941 (transmission).
83. Adler, S., and Theodor, O.: Ann. Trop. Med. 21: 89, 1927 (transmission).
84. Adler, S.: Ann. Trop. Med. 20: 407, 1926 (histopathology).
85. Berlin, C.: Arch. Dermat. & Syph. 41: 874, 1940.
86. Evans, R. B.: Brit. J. Dermat. 50: 17, 1938.
87. Hoare, C. A.: Tr. Roy. Soc. Trop. Med. & Hyg. 32: 67, 1938.
88. Latyshev, N., and Kriukova, A.: Med. Parasit. and Parasitic Dis. Moscow. 11: 74, 1942 (Trop. Dis. Bull. 40: 296, 1943).
89. Laveran, A.: Bull. Soc. path. exot. 8: 363, 1915.
90. Sergeant, Ed., Sergeant, Et., Parrot, L., Donati, A., and Béguet, M.: Compt. rend. Acad. de sc. 173: 1030, 1921.
91. Wright, J. H.: J. Med. Res. 10: 472, 1903-04.

Malaria

92. Anderson, W. A. D., Morrison, D. B., and Williams, E. F., Jr.: Arch. Path. 33: 589, 1942.
- 92a. Shortt, H. E., Garnham, P. C. C., and Covell, G.: Brit. M. J. 2: 547, 1948 (exoerythrocytic phase).
93. Bruetsch, W. L.: Am. J. Psychiat. 12: 19, 1932 (histopathology).
94. Burowa, L.: Arch. f. Schiffs- u. Tropen-Hyg. 37: 408, 1933.
95. Coggesshall, L. T.: Medicine 22: 87-102, 1943 (immunity in malaria).
96. Daniel, R. A., Jr.: Ann. Surg. 111: 436, 1940.
97. Dhayagude, R. G., and Purandare, N. M.: Arch. Path. 36: 550, 1943 (cerebral malaria).
98. Huff, C. G., and Coulston, F.: J. Infect. Dis. 75: 231, 1944.
99. Klotz, O.: Am. J. Trop. Med. 9: 241, 1929 (necrosis of the liver in malaria).
100. Knisely, M. H., and Bloch, E. H.: Proc. Inst. Med. Chicago, Vol. 15, No. 13, 1944.
101. Lafora, G. R.: J. f. Psychol. u. Neurol. 19: 209, 1912.
102. Mohr, W.: Arch. f. Schiffs- u. Tropen-Hyg. 44: 521, 1940.
103. Morrison, D. B., and Anderson, W. A. D.: Pub. Health Rep. 57: 90, 1942.
104. Moulton, F. R., editor: A Symposium on Human Malaria; with Special Reference to North America and the Caribbean Region. Amer. Assoc. Adv. Sc. No. 15, Washington, D. C., 1941.
105. Ridgon, R. H.: South. M. J. 37: 687, 1944.
106. Sergeant, Ed., Sergeant, Et., Parrot, L., and Donati, A.: Tr. Roy. Soc. Trop. Med. & Hyg. 27: 277, 1933.

107. Taliaferro, W. H., and Mulligan, H. W.: Indian Med. Res. Memoirs, No. 29, Suppl. series to the Indian J. Med. Rec., pp. 138, 1937 (histopathology of malaria).
108. Tarejev, E. M., Gontayeva, A. A., and Rotenberg, S. S.: Trop. Dis. Bull. 41: 257, 1944.

Blackwater Fever

109. Barratt, J. O. W., and Yorke, W.: Ann. Trop. Med. 3: 1, 1909.
110. Dameshek, W.: J. A. M. A. 123: 77, 1943.
111. Fairley, N. H., and Bromfield, R. J.: Tr. Roy. Soc. Trop. Med. & Hyg. 28: 141, 1934.
112. Fernan-Nunez, M.: Am. J. Trop. Med. 16: 563, 1936.
113. Giglioli, G.: Tr. Roy. Soc. Trop. Med. & Hyg. 26: 204, 1932.
114. Macgrath, B.: Tr. Roy. Soc. Trop. Med. & Hyg. 37: 1, 1944.
115. Oliver-González, J.: Proc. Soc. Exper. Biol. & Med. 57: 25, 1944.
116. Ross, G. R.: London Sch. of Hyg. and Trop. Med. Mem. Series, No. 6, 1932, pp. 262.
117. Stephens, J. W. W.: Blackwater Fever, London, 1937, University Press of Liverpool, Hodder and Stoughton Ltd., p. 727.
118. Thomson, J. G.: London Sch. Trop. Med. Research Memoir Series, Vol. VI, 1924, pp. 149.

Balantidiasis

119. Ratcliffe, H. L.: Am. J. Hyg. 19: 68, 1934.
120. Strong, R. P.: Bureau Govt. Labs. Bull. Manila, P. I. Pub. No. 26, pp. 77, 1904.
121. Walker, E. L.: Philippine J. Sc. (B) 8: 333, 1913.

Distomiasis

122. Africa, C. M., de León, W., and García, E. Y.: Acta Medica Philippina. Monogr. Series No. 1, pp. 132, 1940.
123. Faust, E. C., and Khaw, O. K.: Am. J. Hyg., Monogr. Series No. 8, pp. 284, 1927.
124. Kouri, P., Basnuevo, J. I., Sotolongo, F., and Anido, V.: Rev. de med. trop. y parasitol. 4: 185, 1938.
125. Miller, J. J., Jr., and Wilbur, D. L.: U. S. Nav. Med. Bull. 42: 108, 1944.
126. Vogel, H.: Arch. f. Schiffs- u. Tropen-Hyg. 40: 181, 1936.

Schistosomiasis

127. Bayoumi, M. L.: J. Egyptian Med. Assoc. 22: 457, 1939 (bilharzial myelitis).
128. Brumpt, E.: Ann. de parasitol. 8: 263, 1930.
129. Brumpt, E.: Ann. de parasitol. 8: 75, 1930 (bilharzial cancer).
130. Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, 1940, Lea & Febiger.
131. Cram, Eloise B., Jones, Myrna F., and Wright, W. H.: Science 101: 302, 1945.
132. Fairley, N. H.: Brit. M. J. 2: 983, 1931.
133. Faust, E. C., and Meleney, H. E.: Am. J. Hyg. Monographic Ser. No. 3, 1924, pp. 339.
134. Girges, Rameses: Schistosomiasis (Bilharziasis), London, 1934, John Bale, Sons & Danielsson, Ltd., p. 529.
135. Hoeppi, R.: Chinese M. J. 46: 1179, 1932.
136. Hoff, H., and Shaby, J. A.: Tr. Roy. Soc. Trop. Med. & Hyg. 33: 107, 1939.
137. Kohlschütter, E., and Koppisch, E.: Schweiz. Ztschr. f. Path. u. Bakt. 4: 357, 1941.
138. Koppisch, E.: Puerto Rico J. Pub. Health & Trop. Med. 13: 1, 1937 (pathologic anatomy of experimental schistosomiasis mansoni).
139. Koppisch, E.: Puerto Rico J. Pub. Health & Trop. Med. 16: 395, 1941 (morbid anatomy).
140. Nessmann, V., and Trensz, F.: Ann. de parasitol. 6: 182, 1928.
141. Ponce, Angel M.: Personal communication, 1943.
142. Pons, J. A.: Puerto Rico J. Pub. Health & Trop. Med. 13: 171, 1937-38 (clinical aspects).
143. Shaw, A. F. B., and Ghareeb, A. A.: J. Path. & Bact. 46: 401, 1938 (pulmonary schistosomiasis).
144. Vogel, H.: Arch. f. Schiffs- u. Tropen-Hyg. 36: 384, 1932.

Taeniasis Solium

145. Brailsford, J. F.: Brit. J. Radiol. 14: 79, 1941 (radiographic detection of cysticercus).
146. Dixon, H. B. F., and Smithers, D. W.: Quart. J. Med. 27: 603, 1934 (epilepsy in cysticerosis).
147. Doigopol, Vera B., and Neustaedter, M.: Arch. Neurol. & Psychiat. 33: 132, 1935.
148. MacArthur, W. P.: Tr. Roy. Soc. Trop. Med. & Hyg. 27: 343, 1934 (cysticercosis).
149. Ménon, T. B., and Veliah, G. D.: Tr. Roy. Soc. Trop. Med. & Hyg. 33: 537, 1940 (tissue reactions to cysticercus).
150. Ochoterena, I.: An. Inst. Biol. Univ. Nac. México 6: 79, 1935.

Echinococcosis

151. Arce, J.: Arch. Surg. 42: 1, 1941.
152. Bacaloglu, C., Balan, N., Ballif, L., and Vasilescu, C.: Ann. Medicine 26: 242, 1929.
153. Culbertson, J. T.: Immunity Against Animal Parasites, New York, 1941, Columbia University Press, p. 274.
154. Dévé, F.: Arch. de méd. d. e'enf., Par. 21: 225, 1918.
155. Dew, H. R.: Hydatid Disease: Its Pathology, Diagnosis and Treatment, Sydney, 1928, The Australasian Medical Publishing Company, Ltd., p. 429.
156. Fairley, K. D.: M. J. Australia 1: 472, 1929 (intradermal test).
157. Fairley, K. D., Fairley, N. H., and Williams, F. E.: M. J. Australia 2: 320, 1929 (intradermal test).
158. Godfrey, M. F.: Arch. Int. Med. 60: 783, 1937.
159. Morenas, L.: Compt. rend. Soc. de biol. 110: 321, 1932.
160. Rose, H. M., and Culbertson, J. T.: J. A. M. A. 115: 594, 1940.
161. Zerbino, V.: Rev. méd. del Uruguay 22: 695, 1919. Abstract in J. A. M. A. 74: 213, 1920.

Diphyllobothriasis

162. Birkeland, I. W.: Medicine 11: 1, 1932.

Ascariasis

163. Girges, R.: J. Trop. Med. & Hyg. 37: 296, 1934.
164. Ransom, B. H., and Cram, E. B.: Am. J. Trop. Med. 1: 129, 1921.

Enterobiasis

165. Aschoff, L.: Med. Klin. 9: 249, 1913.
166. Cram, Eloise B., and Reardon, Lucy: Am. J. Hyg. Section D 29: 17, 1939.
167. Goodale, R. H., and Krischner, H.: Arch. Path. 9: 631, 1930.
168. Gordon, H.: Arch. Path. 16: 177, 1933.
169. Nolan, M. O., and Reardon, Lucy: J. Parasitol. 25: 173, 1939.
170. Penso, G.: Ann. de Parasit. 10: 271, 1932.
171. Wu, L. C.: Chinese M. J. 49: 256, 1935.

Strongyloidiasis

172. Faust, E. C.: J. A. M. A. 98: 2276, 1932.
173. Faust, E. C., and De Groat, A.: Am. J. Trop. Med. 20: 359, 1940.

Ancylostomiasis

174. Ashford, B. K., Payne, G. C., and Payne, Florence K.: J. A. M. A. 101: 843, 1933.
175. Ashford, B. K., and Gutiérrez Igarrávídez, P.: Senate Document No. 808, Washington, Government Printing Office, 1911, p. 335.
176. Bonne, C.: Am. J. Trop. Med. 22: 507, 1942.
177. Cruz, W. O.: Mem. Inst. Oswaldo Cruz 27: 423 (Portuguese), 454 (English), 1933.
178. Cruz, W. O.: Mem. Inst. Oswaldo Cruz 28: 423 (Portuguese), 454 (English), 1933.
179. Keller, A. E., Leathers, W. S., and Ricks, H. C.: Am. J. Hyg. 19: 629, 1934.
180. Kendrick, J. F.: Am. J. Trop. Med. 14: 363, 1934.
181. Kirby-Smith, J. L., Dove, W. E., and White, G. F.: Arch. Dermat. & Syph. 18: 137, 1926 (creeping eruption).

182. Peña Chavarría, A., and Rotter, W.: Arch. f. Schiffs- u. Tropen-Hyg. **39**: 505, 1935.
 183. Rhoads, C. P., Castle, W. B., Payne, G. C., and Lawson, H. A.: Am. J. Hyg. **20**: 291, 1934 (hookworm anemia).
 184. Scott, R. B.: Lancet **2**: 549, 1938.
 185. White, G. F., and Dove, W. E.: J. A. M. A. **90**: 1701, 1928 (creeping eruption).
 186. Wright, D. O., and Gold, E. M.: J. A. M. A. **128**: 1082, 1945 (Loeffler's syndrome associated with creeping eruption).

Filariasis

187. Anderson, J.: London School of Tropical Medicine Research Memoir Series. Memoir 7, Vol. 5, 1924.
 188. Culbertson, J. T.: Immunity Against Animal Parasites, New York, 1941, Columbia University Press, p. 274.
 189. Culbertson, J. T., Rose, H. M., and Demarest, Constance R.: Am. J. Hyg. **39**: 156, 1944.
 190. Dhayagude, R. G., and Amin, B. M.: Am. J. Path. **18**: 351, 1942.
 191. Dickson, J. G., Huntington, R. W., Jr., and Eichold, S.: U. S. Nav. M. Bull. **41**: 1240, 1943.
 192. Ferrer, J. C.: J. Urol. **32**: 710, 1934.
 193. Grace, A. W., and Grace, Feiga B.: London School of Hygiene and Trop. Med. Research Memoir Series. Memoir No. 3, pp. 75, 1931.
 194. Knott, J.: Tr. Roy. Soc. Trop. Med. & Hyg. **29**: 59, 1935.
 195. Lane, C.: Lancet **1**: 1291, 1929.
 196. Lane, C.: Lancet **2**: 399, 1933.
 197. Makar, N.: J. Egyptian M. Assoc. **21**: 682, 1938.
 198. Michael, P.: U. S. Nav. M. Bull. **42**: 1059, 1944.
 199. Morales-Otero, P., and Pomales-Lebrón, A.: Tr. Roy. Soc. Trop. Med. Hyg. **30**: 191, 1936.
 200. Napier, L. E.: Medicine **23**: 149, 1944.
 201. O'Connor, F. W.: Puerto Rico J. Pub. Health & Trop. Med. **6**: 263, 1931.
 202. O'Connor, F. W., and Hulse, Constance, R.: Tr. Roy. Soc. Trop. Med. & Hyg. **25**: 445, 1932.
 203. O'Connor, F. W.: Trans. Roy. Soc. Trop. Med. & Hyg. **26**: 13, 1932.
 204. O'Connor, F. W., and Hulse, Constance, R.: Puerto Rico J. Pub. Health & Trop. Med. **11**: 167, 1935.
 205. Rose, H. M., Culbertson, J. T., and Lipman, Miriam, O.: J. Clin. Investigation **24**: 532, 1945.
 206. Zuckerman, S. S., and Hubbard, J. S.: U. S. Nav. M. Bull. **44**: 27, 1945.

Onchocerciasis

207. Appelmans, M.: Rev. belge sc. méd. **7**: 525, 1935.
 208. Blacklock, D. B.: Ann. Trop. Med. **20**: 1, 1926.
 209. D'Hooghe, M.: Ann. Soc. belge de méd. trop. **14**: 153, 1934.
 210. D'Hooghe, M.: Ann. Soc. belge de méd. trop. **15**: 159, 1935.

211. Hoffmann, C. C.: Arch. f. Schiffs- u. Tropen-Hyg. **34**: 461, 1930.
 212. Ochoterena, I.: An. Inst. Biol. Univ. Nac. México **1**: 205, 1930.
 213. Quevedo, A.: Am. J. Ophth. **24**: 1185, 1941.
 214. Robles, R.: Bull. Soc. path. exot. **12**: 442, 1919.
 215. Strong, R. P., Sandground, J. H., Bequaert, J. C., and Muñoz Ochoa, M.: Onchocerciasis. With Special Reference to the Central America Form of the Disease, Cambridge, 1934, Harvard University Press, p. 234.
 216. Strong, R. P., Hissette, J., Sandground, J. H., and Bequaert, J. C.: Am. J. Trop. Med. Suppl. **18**: 1, 1938.
 217. van den Berghe, L.: Ann. Soc. belge de méd. trop. **16**: 549, 1936.

Loiasis

218. Klotz, O.: Am. J. Trop. Med. **10**: 57, 1930.
 219. Connal, A., and Connal, S. L. M.: Tr. Roy. Soc. Trop. Med. & Hyg. **16**: 64, 1922.

Dracunculiasis

220. Fairley, N. H., and Liston, W. G.: Indian J. M. Research **11**: 915, 1924.
 221. Fairley, N. H.: Ibid. **12**: 351, 1924.

Trichiniasis

222. Blumer, G.: Yale J. Biol. & Med. **11**: 581, 1939.
 223. Dunlap, G. L., and Weller, C. V.: Proc. Soc. Exper. Biol. & Med. **30**: 1261, 1932-33 (myocarditis).
 224. Gould, S. E.: Trichinosis, Springfield, Ill., 1945, Charles C Thomas.
 225. Hassin, G. B., and Diamond, I. B.: Arch. Neurol. & Psychiat. **15**: 34, 1926 (encephalitis).
 226. Lewis, W. L., Boller, Anna E., Hoskins, H. P., Merillat, L. A., and Smith, H. R.: J. A. M. A. **114**: 35, 1940.
 227. McCoy, O. R.: Am. J. Hyg. **14**: 484, 1931.
 228. Most, H., and Abeles, M. M.: Arch. Neurol. & Psychiat. **37**: 589, 1937 (nervous system).
 229. Theiler, H., Augustine, D. L., and Spink, W. W.: Parasitology **27**: 345, 1935 (eosinophilia).
 230. Terry, L. L., and Work, J. L.: Am. Heart J. **19**: 478, 1940 (trichinosis of the myocardium).
 231. Von Herrenschwand, F.: Arch. f. Ophth. **119**: 374, 1927.
 232. Wright, W. H.: Am. J. Pub. Health **29**: 119, 1939 (epidemiology).
 233. Zenker, F. A.: Virchows Arch. f. path. Anat. **18**: 561, 1860.

Trichuriasis

234. Getz, L.: Am. J. Dis. Child. **70**: 19, 1945.

Chapter 17

VITAMINS AND DEFICIENCY DISEASES

HENRY PINKERTON

Introduction

With advancing knowledge of the complex biochemical mechanisms involved in vital processes it has become increasingly difficult to define and classify the important group of "accessory food substances" commonly known as vitamins. A sharp dividing line between vitamins and certain of the essential amino acids is not easily established. For practical purposes, we may define vitamins as organic catalysts of exogenous origin, which are effective in relatively minute amounts, and which are essential for the maintenance of the normal structure and function of cells and organisms. Vitamins are not utilized to furnish energy, but act rather as essential components of the chemical machinery by means of which the true food substances are metabolized. Since they are not synthesized in the body, they must be supplied in the diet, or from other external sources. Some compounds are vitamins, in the above defined sense, for practically all forms of living matter, while others are vitamins only for those cells or organisms which are unable to manufacture them.

Details concerning the chemistry of the vitamins, their sources, quantitative requirements for prophylaxis and therapeutics, etc., will be found in textbooks of biochemistry and medicine. We are concerned here primarily with vitamins as they are related to pathologic processes. A brief discussion of their physiologic action is, however, necessary for the understanding of these relationships.

Mechanism of Action of Vitamins.—Modern investigation has shown that the biological action of many (perhaps all) vitamins is intimately related to intracellular enzyme systems.¹ Certain vitamins represent those constituents of essential enzymes (usually constituents of the prosthetic groups) which the cells are unable to synthesize. It has, moreover, become clear that many endocrine products (hormones) likewise act through the medium of the intracellular enzyme systems, either by entering into such systems, or by stimulating or inhibiting

them.² The essential difference between hormones and vitamins is that the former are endogenous (synthesized in certain organs for the maintenance of others) while the latter are of exogenous origin. The failure of certain enzyme systems has also been shown to depend on the inheritance of defective genes.³

Although the definitely known activities of vitamins are for the most part concerned with catabolic processes in cells, it must be remembered that most enzyme systems have reversible action, and it is probable that many vitamins are also important in systems which build up the specific proteins characteristic of each type of cell.

Thus, living cells, with normal genic composition and with the aid of hormones and vitamins, may be said to construct and maintain the cytological machinery which carries out the complex metabolic reactions necessary for their normal life, function, and reproduction. Students of enzymes, genes, hormones, and vitamins, in their efforts to learn the details of these vital processes, are meeting today on common ground, and the intricate picture of intracellular metabolism is slowly being developed. Histochemical studies of vitamins and enzymes are furnishing important information concerning their location in cells and their alterations in pathological states.^{4, 5}

Sources, Requirements, and Modern Uses of Vitamins.—Most vitamins are primarily of plant origin and normally enter the body as constituents of ingested plant or animal food. In modern life they are added to the diet or injected parenterally in concentrated or pure form, for both prophylactic and therapeutic purposes. The minimum quantitative requirements of many vitamins for the maintenance of health in normal individuals have been more or less accurately established, the range being from a fraction of a milligram to about 50 mg. The therapeutic dosage necessary to correct certain pathologic states has also been determined in many instances, and may be many times the prophylactic dose.

While a moderate excess over the minimum requirements is desirable for normal people, there is definite evidence that large doses of vitamin D are harmful, and some evidence that damage may result from excessive doses of vitamin A.

Paths of Investigation in Man and Animals.—Early knowledge of vitamin deficiency was obtained largely by clinical observation of disease entities, and empirical discovery that certain foods had preventive or curative value. With the extensive study of dietary deficiencies

in experimental animals, the complexity of the problem became evident. In recent years, the isolation of vitamins in chemically pure form has led to the determination of structural formulas, and eventually in many instances to chemical synthesis. The final step, the determination of the mode of action, has been taken in the case of several vitamins.

The pathologic lesions resulting from vitamin deficiencies are of two types: primary changes caused by metabolic disturbance in the tissues or organs physiologically served by the vitamin involved, and secondary effects (notably inanition, organ atrophy, and arrest of growth) on the body as a whole.

Morphologic studies of the primary types of lesions have played a most important part in vitamin research, particularly in connection with our understanding of the physiologic action of vitamins. Since vitamins often control the function of specific types of tissue, it has been possible to study not only the retrograde changes, resulting from deficiency, but also the mechanisms of repair which occur when the deficiencies are corrected. Studies of this type, though in their infancy, already have made unique contributions to our knowledge of normal cell physiology.⁶

Simple and Conditioned Deficiency.—A vitamin deficiency may be said to be simple when it occurs in a normal individual as a result of inadequate dietary intake. Deficiencies resulting from nutritional disturbances brought about by unrelated pathologic conditions are known as "conditioned" deficiencies.

Vitamins must reach the interior of cells in order to exert their functions. Lesions and symptoms of deficiency may result from a variety of causes which interfere with their arrival in the cells in sufficient amounts or with their function after arriving there. These include destruction of the vitamins by antagonistic action of other dietary constituents and failure of absorption from the intestinal tract because of vomiting, diarrhea, fixation by other agents, or pathologic changes in the mucosa. Increased requirement because of an increase in the metabolic rate (as in fever or hyperthyroidism) must also be mentioned. Even though vitamins may be absorbed and reach the cells, their utilization may be subnormal because of abnormalities in the cells themselves. Parenteral injection of crystalline vitamins will overcome difficulties in intestinal absorption, but not those due to disturbed cellular physiology.

It has already been brought out that vitamins function by entering into complex cytological mechanisms which involve also enzymes, hormones, and genes. Important vital processes such as detoxification and immune body formation are implemented by these mechanisms. A consideration of these facts makes it clear that symptoms of "conditioned" deficiency may appear as a result of disturbances of cellular metabolism from many different causes. It is probable that viruses, because of the profound changes which they induce in cells, may interfere with the mechanisms discussed above, and thus bring about symptoms of vitamin deficiency in spite of adequate dietary intake or parenteral injection. Our knowledge of

the interrelationships of genes, enzymes, vitamins, hormones, and viruses is rudimentary.

Antivitamins.—Chemical compounds which are closely related to vitamins will in some cases replace active vitamins in enzyme systems and thus produce the effects of vitamin deficiencies. Analogs acting in this way have been discovered for ascorbic acid, nicotinic acid, riboflavin, thiamine, and folic acid. Folic acid analogues have been extensively studied because they are temporarily beneficial in certain cases of acute leukemia.⁷ Quite different in their mode of action are certain enzymes which destroy vitamins. The best known example of the latter is thiaminase, which is present in certain types of raw fish, and which has been responsible for a rapidly fatal disease in foxes known as Chastek paralysis.⁸

Nomenclature and Classification of Vitamins.—Vitamins differ widely in chemical composition and physiologic action, having little in common except their exogenous origin and their importance in cellular physiology. Originally they were named by assigning letters of the alphabet to them. This system proved satisfactory during the earlier period of growth of knowledge concerning them. Vitamins A, B, C, and D became well established, but soon new letters were being applied to incompletely studied nutritional factors which proved to be identical. Vitamin B has been found to be composed of a number of chemically specific factors with variable physiologic action. These components are best referred to by their specific chemical names, or at least by names indicative of their chemical nature. The entire B group, consisting of some twenty-two known components and probably of others as yet undiscovered, is best called vitamin B complex. •

Chemical names have also to some extent replaced letters for the nomenclature of vitamins other than those of the B group, but the alphabetical designation is still widely used. All of the well-recognized vitamins are included under the following headings: Vitamin A, Vitamin B Complex (composed of many specific factors), Vitamin C (ascorbic acid), Vitamin D, Vitamin E (alpha tocopherol), and Vitamin K.

Vitamins A, D, E, and K are fat soluble, while vitamin C and the members of the B complex are water soluble. This distinction has little value for purposes of nomenclature or classification.

The diseases caused by specific vitamin deficiencies are often called the *avitaminoses*. In avitaminosis A, xerophthalmia and night blindness are the usual clinical manifestations. Beriberi and Wernicke's disease are associated rather specifically with deficiency of one member of the B group of vitamins—namely, thiamine. Pellagra is apparently caused by deficiency of several elements of the B complex, but particularly by niacin deficiency. The clinical picture of ariboflavinosis is fairly well recognized. Avitaminosis C is scurvy or scorbutus. Avitaminosis D includes rickets and osteomalacia. No disease in man has been proved to result from vitamin E deficiency. Avitaminosis K causes hemorrhages under certain conditions.

Vitamin A

Chemistry and Physiology.—Vitamin A is a fat-soluble colorless primary alcohol which is derived from certain yellow plant pigments known as carotenes. At least two chemically distinct types of vitamin A are recognized, but the two types, as far as present knowledge goes, are physiologically identical. The carotene molecules are composed of a long chain of carbon and hydrogen atoms, with a ring at each end. In the liver these carotene molecules are split in the center to form, with the addition of two molecules of water, two molecules of vitamin A. Vitamin A may enter the body either as such or in the form of its precursors, the carotenes. Fish-liver oils are important sources of vitamin A itself, while the carotenes are primarily of vegetable origin. In cirrhosis of the liver, the rate of formation of vitamin A from the carotenes may be reduced.

By means of ultraviolet light, vitamin A can be demonstrated as a fluorescent substance in microscopic sections of animal tissues.⁹ By this method, it has been shown to be associated with lipoid droplets in the liver, adrenal cortex, testicle, ovary, adipose tissue, lactating breast, and other tissues.

The known physiologic activities of vitamin A are: (1) The maintenance, by a mechanism as yet undiscovered, of the structure and function of certain of the specialized types of epithelium. (2) The formation, by combination with a protein, of photosensitive pigments in the rods and cones of the retina known as visual purple and visual violet. (3) The maintenance of normal skeletal growth.

Lesions Resulting From Deficiency of Vitamin A.—The most characteristic effects of experimental vitamin A deficiency are seen in epithelial structures.⁶ Many types of epithelium, including that of the salivary glands, the respiratory tract, the genitourinary tract, the pancreatic ducts, the skin, the conjunctivae, and the enamel organs of the teeth are affected. The epithelial cells involved undergo atrophy,

reparative proliferation of the basal layer, and then, regardless of their original structure and function, replacement by stratified keratinizing epithelium. Correction of the deficiency results in autolysis of the keratinized cells and restoration of the original type of epithelium by differentiation of the persisting basal layer.

Vitamin A deficiency in experimental animals causes cessation of endochondral growth, but periosteal bone formation continues normally, so that the long bones become shorter and thicker.¹⁰ Wolbach and Bessey¹¹ have shown that paralysis and nerve degeneration result not from a direct effect of the deficiency on nerve tissue, but from continued growth of the central nervous system after skeletal growth has been arrested. This disproportionate growth rate causes overcrowding of the cranial cavity and spinal cord, with resulting herniation of the brain tissue and nerve roots into the venous sinuses and intervertebral foramina. In this way mechanical damage and degeneration of nervous tissue is brought about.

In man, many of the experimental lesions are duplicated. Retarded growth is seen in children, and emaciation at all ages. There is atrophy of the skeletal muscles and lymphatic tissue, and moderate anemia, probably as a result of bone marrow atrophy.

Xerophthalmia, a dry scaly lesion of the scleral conjunctiva, is the most obvious lesion and often establishes the diagnosis during life. Corneal ulceration eventually occurs, with consequent bacterial infection (keratomalacia). Melanotic pigmentation of the cornea is often seen.

The most characteristic type of skin lesion is *follicular hyperkeratosis*. Multiple, firm papules, 1 to 5 mm. in diameter, which may be almost confluent, develop as a result of the formation of keratin plugs in the sebaceous glands, giving the characteristic "toad skin" appearance (Fig. 297). Dryness and sealiness of the skin and furunculosis are also commonly present. These skin lesions have been described only in adults. Histologically, degeneration of the sweat glands and hyperkeratinization of the ducts and hair follicles is seen (Fig. 298).

Squamous metaplasia is most often seen in the trachea and bronchi, and pelvis of the kidneys, but the uterus, pancreatic ducts, and certain other epithelial structures may also be affected. Death often results from bronchopneumonia. Obstruction of pancreatic ducts by keratotic plugs may lead to cystic dilatation of the ducts and acini.

Renal calculi are of common occurrence in vitamin A deficient animals. In man, however, there is no evidence that this deficiency is a common cause of nephrolithiasis.

The effect of vitamin A deficiency on human teeth is not yet entirely clear. In the continuously growing incisor teeth of rats and guinea pigs, important abnormalities occur as a result of atrophy and squamous metaplasia of the enamel organ. Similar changes in the tooth germs of an infant have been described.¹²

Clinicopathologic Correlation.—The disease occurs at all ages but has a higher morbidity and mortality in infants. It occurs chiefly under dietary conditions approaching starvation.

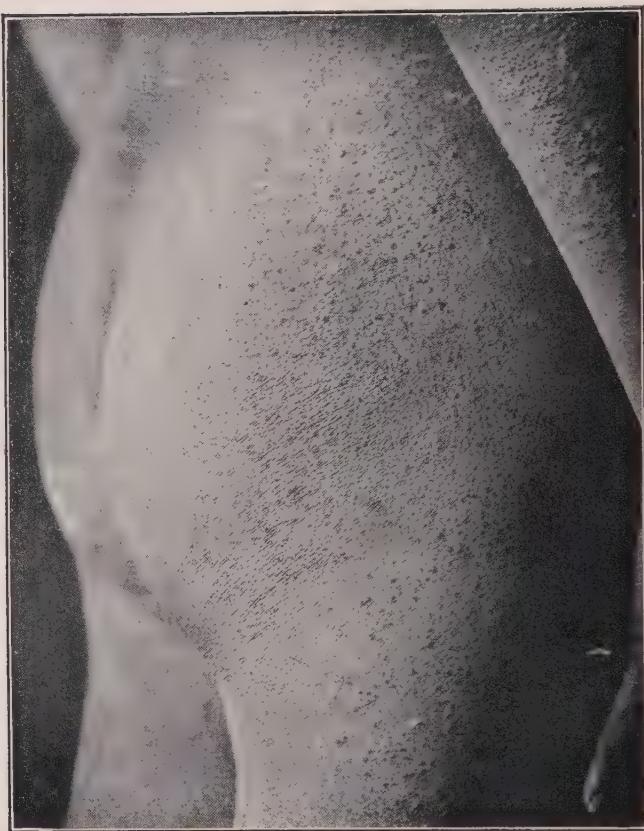


Fig. 297.—Cutaneous lesions in vitamin A deficiency, showing general xeroderma and follicular hyperkeratosis in a Chinese patient with xerophthalmia, before halibut liver oil therapy had been given. (Courtesy Dr. Chester N. Frazier. From Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Co.)



Fig. 298.—Hyperkeratosis of hair follicle in vitamin A deficiency. (Courtesy Dr. Chester N. Frazier. From Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Co.)

The papular cutaneous lesions, which are seen chiefly in adults, are most numerous on the thighs and forearms, but may also involve the shoulders, chest, back, and buttocks. Acnelike lesions may appear on the face, but an etiological relationship between vitamin A deficiency and *acne vulgaris* has not been demonstrated.

Bacterial infections, notably conjunctivitis, furunculosis, bronchopneumonia, and pyelonephritis, are common in vitamin A deficiency. There is however no proof that such infections are the result of a specific loss of resistance. The development of infection is always explainable on the basis of mechanical effects consequent to the epithelial changes.

The finding of keratinized epithelial cells in the urine, in vaginal secretions, and in corneal and nasal scrapings is helpful in establishing a diagnosis. Rough chemical tests for vitamin A concentration in the serum have been applied, but these tests do not have quantitative value. The most valuable test for vitamin A deficiency is that in which the speed of adaptation to vision in a feeble light is determined.

In naturally occurring and experimentally produced cirrhosis of the liver, there is decreased conversion of carotene to vitamin A and also

decreased storage of vitamin A. The level of vitamin A in the blood falls markedly, and night blindness is often though not invariably present.

Effect of Excessive Doses.—The administration of large amounts of pure vitamin A to experimental animals accelerates the maturation and degeneration of epiphyseal cartilage, and the remodeling processes. Because of the excessive loss of cortical bone by increased osteoclastic activity (an exaggeration of the normal sequences) multiple fractures occur. Cutaneous lesions also occur, which resemble those seen in deficiency of the B group of vitamins.

Vitamins of the B Group

The term vitamin B was originally applied to a substance capable of curing experimental beriberi, which Funk isolated from rice polishings in 1911. This substance was not chemically pure, and it is now known that thiamine was its most important active component.

Concentrates derived from yeast, wheat germ, rice polishings, and other sources contain a number of factors which collectively are known as the B complex. Some of these are of known chemical nature, while others are known only by their biologic activity.

Much of our knowledge of the specific effects of deficiency of single members of the B group is derived from studies carried out in experimental animals. In order to demonstrate the effect of deficiency of a single component, all other components must be supplied in adequate amounts and the animal must live long enough to become depleted of the component which one desires to study. The effects of riboflavin deficiency, for example, are not seen in animals deprived of the entire B complex. In human beings, although deficiency in several of these factors commonly exists simultaneously, several disease entities are associated more or less specifically with the lack of individual factors. No specific disease is recognized as being due to lack of the entire B complex, and it is therefore desirable to discuss each factor in the group separately. Thiamine deficiency causes *beriberi* and *Wernicke's disease*. Deficiency of niacin (nicotinic acid) is an important factor, though probably not the sole factor, in *pellagra*. The clinical picture of riboflavin deficiency includes "*cheilosis*," a condition characterized by fissures at the angles of the mouth.

Certain effects produced in experimental animals by deprivation of other specific factors will be considered, even though they have not been duplicated in human beings.

The B vitamins, as a group, are characterized by the fact that they are indispensable constituents of all living cells. Certain recently studied compounds, such as biotin, para-aminobenzoic acid, choline, inositol, and folic acid, are considered by many workers to be members of the B group, because they occur in yeast and satisfy the above criterion.

THIAMINE

Chemistry and Physiology.—Thiamine is found in the thermolabile portion of the B complex, while the other members of the B complex which will be considered are thermostable. Thiamine hydrochloride, which was synthesized in 1937, is composed of a pyrimidine base, united to a nitrogen-carbon-sulfur ring containing a pentavalent nitrogen. This compound is phosphorylated to form thiamine pyrophosphate, which acts intracellularly as the coenzyme for carboxylase. The latter enzyme decarboxylates pyruvic acid and participates in the synthesis of fat from carbohydrate. Thus, in thiamine deficiency carbohydrate metabolism is interrupted at the pyruvic acid stage, and pyruvic acid accumulates in the tissues and in the blood. The lesions of thiamine deficiency are not, however, produced by the simple injection of pyruvic acid, and it is probable that the failure of complete combustion of carbohydrate is the important factor, the accumulation of pyruvic acid being incidental.

Lesions Resulting From Deficiency of Thiamine.—The human diseases ascribed to thiamine deficiency are *beriberi* and *Wernicke's disease*. The experimental production in animals by pure thiamine deficiency of the lesions found in these two diseases indicates that deficiency of this vitamin is the major etiological factor.

In fatal cases of *beriberi* the findings are somewhat variable. Grossly, the most common lesions are emaciation, muscular atrophy, dilatation (with or without hypertrophy) of the right side of the heart, generalized edema, serous effusions, and chronic passive congestion of the viscera. Death may be due to cardiac failure or to pneumonia or other complicating infections. The edema is caused in part by cardiac failure, but hypoproteinemia is probably a contributory factor in many cases.¹³ This cardiovascular picture is particularly characteristic of the so-called "wet type" of *beriberi*, which is usually more acute in nature.

Microscopically, loss of striation and fatty degeneration of the myocardial fibers is noted. There is diffuse edema, often with slight lymphocytic infiltration of the interstitial tissue of many organs. Skeletal muscles show hyaline and fatty degenerative changes.

Degenerative changes in nerves (Fig. 299) are more characteristic of the "dry" or chronic

form of the disease, which is seen chiefly in adults. Myelin degeneration and, in severe cases, fragmentation of the axis cylinders are seen in the affected nerves, which may be those of the extremities, the vagi, or the cranial nerves. In thiamine-deficient pigeons, axis cylinder degeneration begins distally and progresses until the neurons are involved.¹⁴ If thiamine is given before neuron death, regeneration of axis cylinders occurs at the usual normal rate. In dogs, similar degenerative changes have been described in the central nervous system.¹⁵



Fig. 299.—Myelin degeneration in a peripheral nerve in a human case of polyneuritis. (From Eddy and Dalldorf, *The Avitaminoses*, Williams and Wilkins Co.)

Wernicke's disease, which is associated with chronic alcoholism, is characterized by ganglion cell degeneration and minute hemorrhagic lesions in the nuclei surrounding the ventricles and aqueduct, particularly the nuclei of the extrinsic muscles of the eye. There is also some reparative proliferation of neuroglial cells. The picture is often complicated by symptoms of beriberi, scurvy, riboflavin deficiency, and pellagra. The original concept that the disease was caused by a toxic effect of alcohol itself has been abandoned. An apparently identical lesion may be produced in thiamine-deficient pigeons.¹⁶ In view of the experimental evi-

dence, thiamine deficiency is now believed to be the most important etiological factor in Wernicke's disease.

Clinicopathologic Correlation.—The mechanism by which thiamine deficiency produces its characteristic lesions is not clear. The degenerative changes in the peripheral nerves and central nervous system are perhaps the result of interrupted carbohydrate metabolism as described above. This seems logical in view of the fact that the metabolism of nervous tissue is believed to be totally dependent on carbohydrate oxidation. No satisfactory explanation of the cardiac manifestations has been advanced.

A diet consisting largely of carbohydrate is an important contributing factor in the development of thiamine deficiency, since thiamine requirements are proportional to carbohydrate combustion.¹⁷ Symptoms of peripheral neuritis and mental confusion are explained on the basis of nervous tissue degeneration, and cardiorespiratory symptoms such as tachycardia, edema, cyanosis, and pulmonary congestion are at least partially explained by the cardiac lesions. Gastrointestinal symptoms, which include vomiting, diarrhea, and epigastric distress, apparently have no satisfactory pathologic basis.

The mortality in beriberi varies from 5 to 50 per cent, depending on the severity of symptoms and on the promptness and adequacy of treatment.

NIACIN (NICOTINIC ACID)

Chemistry and Physiology.—Niacin or nicotinic acid is prepared by oxidizing the alkaloid nicotine. It is betapyridine carboxylic acid. It is water soluble, and occurs as a white crystalline powder. It is commonly used for therapeutic purposes in the form of niacinamide.

Niacin is an essential molecular constituent of two closely related coenzymes (coenzyme I and coenzyme II) which are of primary importance in intracellular oxidation processes.¹⁸ Other as yet undiscovered functions of nicotinic acid will probably be brought to light in the future.

Etiology of Pellagra.—Divergent views still exist concerning the etiology of pellagra, but there is general agreement that the major factor is deficiency of certain members of the B group of vitamins, particularly niacin. Some workers believe that niacin deficiency should be regarded as the cause of pellagra, in spite of the fact that most pellagrins show evidence of multiple deficiencies. The pathologic changes of uncomplicated niacin deficiency have not been described in either man or experimental animals. Those lesions which heal on administration of niacin are assumed to have been caused by lack of that compound. Pellagra is apparently a nutritional disease of the "conditioned" type, conditioning factors including exposure to sunlight, alcoholism, organic diseases, infectious diseases, and other factors which have not yet been evaluated.¹⁹ About 50 per cent of pellagrins show achlorhydria. Qualitative deficiency in the amino acid composition of the protein supply is probably a conditioning factor in pellagra. The relation of a corn-meal diet to pellagra is probably explain-

able on the basis of the fact that corn meal is deficient in tryptophane, which is a precursor of nicotinic acid. There is also some evidence the corn meal may contain an antagonist of nicotinic acid.²⁰

The mucous membrane lesions and the gastrointestinal and mental symptoms usually respond promptly to niacin administration. Certain residual signs and symptoms are of the type associated with thiamine or riboflavin deficiency, and these often respond to the appropriate treatment.

Coenzymes I and II, which have an abnormally low value in the blood and urine of pellagrins, rise to normal levels or higher when niacin is given.

Lesions Resulting From Deficiency.—The pathologic lesions of pellagra involve the skin, the mucous membranes, the gastrointestinal tract, and the nervous system.

The cutaneous lesions, which may be absent in some cases, are seen particularly in areas exposed to sunlight, but may occur in any regions exposed to irritation. They show a striking tendency to symmetrical distribution, and the affected areas are sharply demarcated from the normal. In the early stages, the lesions resemble sunburn, but later the skin becomes roughened, keratotic, scaly, and pigmented (Fig. 300). Microscopically,²¹ one sees congestion of



Fig. 300.—Pellagra. Dermatitis and pigmentation of back of hand. (Courtesy Dr. Grover W. Wende. From Sutton and Sutton, Diseases of the Skin, The C. V. Mosby Co.)

the papillary blood vessels, and edema of the papillae. There is moderate lymphocytic infiltration in the corium. The most striking feature is the marked thickening of the keratinized layer of the epidermis.

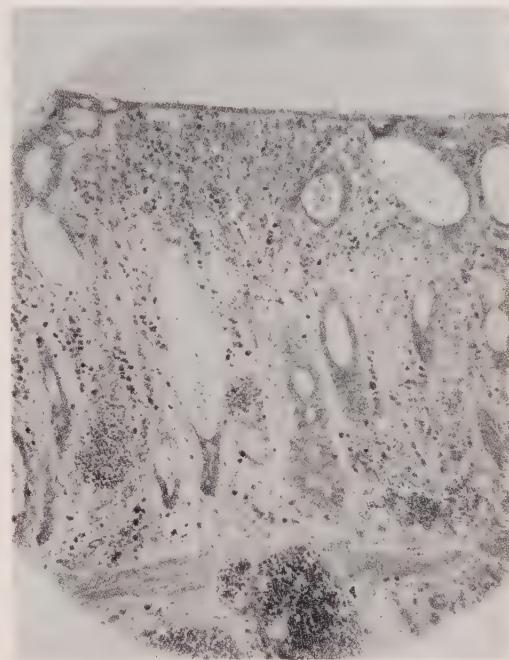


Fig. 301.—Lesion in the colon from a human case of pellagra. Photograph of a specimen from the collection of Dr. James Denton illustrating the cystic glands which are characteristically found in pellagra, sprue, and possibly other related deficiency diseases. The lesion was formerly known as colitis cystica superficialis and was associated with malnutrition. (From Eddy and Dahlhoff, The Avitaminoses, Williams and Wilkins Co.)

The tongue, buccal membranes, gums, and palate become swollen and red, with eventual ulceration. Infection with Vincent's organisms often causes a gray membrane to form. Microscopically the lesions resemble those of the skin.

In the intestinal tract, particularly the colon, there is seen thickening of the wall, with edema and lymphocytic infiltration. Membranous enteritis, with or without ulceration, is often present. Atrophy and cystic dilatation of the crypts of Lieberkühn are said to be characteristic.²² (Fig. 301.)

Lesions in the nervous system appear late in the course of the disease. Demyelination of the posterior and lateral columns of the spinal cord and focal demyelination and ganglion cell degeneration in the cerebrum have been described.²³

The possible occurrence of simultaneous lesions of beriberi, ariboflavinosis, etc., has already been mentioned. Nonspecific lesions seen post mortem may include generalized emaciation, visceral atrophy, fatty infiltration of the liver, and terminal bronchopneumonia.

The key to the production of certain of the lesions in pellagra is undoubtedly the role of niacin in cellular oxidation processes, but this physiologic principle has not been translated into terms which explain clearly the specific lesions found. No general principle comparable to the concept of epithelial integrity in vitamin A deficiency, intercellular substance maintenance in ascorbic acid deficiency, etc., can be set forth on the basis of present evidence.

RIBOFLAVIN

Riboflavin (empirical formula $C_{17}H_{20}N_4O_6$) was isolated in 1933 and synthesized in 1935. Historically it was the first vitamin to be identified as a constituent of an enzyme system. It forms the prosthetic group of several flavo-



Fig. 302.—Vascularization of the cornea due to riboflavin deficiency. Photograph of a rat eye which was injected with India ink to demonstrate the plexus of newly formed blood vessels. (From Eckardt and Johnson: Arch. Ophth. 21: 315, 1939.)

protein enzymes, including the "yellow respiratory enzyme" (Warburg and Christian) now known as cytochrome oxidase, which together with the cytochromes forms an enzyme system of outstanding importance in cellular respiration.

The lesions of riboflavin deficiency in young rats are produced only after a period of several weeks during which all other dietary factors are present in adequate amounts. Depletion will not occur if rats are allowed to eat their feces, since the intestinal bacteria synthesize considerable amounts of riboflavin. Failure to gain weight, progressive loss of hair, and swelling and redness of the ears and paws are the outstanding external manifestations. In the late stages extreme weakness and coma develop, with respirations only one or two per minute. From this moribund state rats recover almost instantaneously a considerable amount of vitality and strength when small doses of crystalline riboflavin are injected. This dramatic result is apparently due to the sudden resumption of intracellular respiration.

Vascularization of the cornea by capillary sprouts from the limbic plexus (Fig. 302) was first noted in riboflavin-deficient rats,²⁴ and later recognized as an important and early sign of deficiency of this vitamin in man.²⁵ In the later stages conjunctivitis develops. The ingrowth of capillaries into the normally avascular cornea probably is an attempt to compensate for the breakdown of oxidation processes in the corneal cells. The ocular lesions in man and in experimental animals progress to the formation of keratitis and ulceration of the cornea.

Ariboflavinosis in man is characterized also by "cheilosis" (fissure formation and crusts at the angles of the mouth) and by redness and irritation of the lips.²⁶ Of less constant occurrence are circumoral pallor and seborrheic dermatitis of the nasolabial folds and ears. (See Fig. 303.) Rarely the dermatitis has a



Fig. 303.—Ariboflavinosis. Cheilosis, nasolabial lesion and the blepharospasm. (From Sydenstricker et al.: J. A. M. A. 114: 2437, 1940.)

more generalized distribution. Riboflavin deficiency may occur in a pure form, or in patients suffering from pellagra, or from various multiple deficiencies.

Riboflavin deficiency in pregnant rats has been shown to cause a variety of congenital abnormalities in the offspring, including cleft palate and club foot.²⁷ The role of nutritional factors in the production of congenital abnormalities in man has not been extensively studied.

PYRIDOXINE (B₆)

Pyridoxine, a pyridine derivative, with the empirical formula C₈H₁₁NO₃, was differentiated from other heat-stable members of the B complex by Györgyi and his co-workers²⁸ in 1933. These workers showed that a characteristic dermatitis in rats is caused specifically by the absence of this vitamin. The paws, snout, and ears become hyperemic and swollen, with eventual desquamation and ulceration. Although the dermatitis has been described as "acrodynia-like," there is no evidence that human acrodynia is caused by pyridoxine deficiency.

In several experimental animals, including pigs, prolonged pyridoxine deficiency causes severe microcytic anemia, which is improved, but not entirely alleviated, by the administration of pyridoxine. Other lesions found in experimental animals are demyelination of peripheral nerves, dorsal root ganglia, and dorsal columns of the spinal cord, and fatty infiltration and hemosiderosis of the liver.

The importance of pyridoxine in human nutrition is not clear at present. Certain residual symptoms in pellagrins occasionally respond to pyridoxine administration.²⁹ As in the case of many other vitamins, empirical evidence has suggested possible therapeutic value in a variety of clinical conditions, but evaluation of such evidence is difficult.

PANTOTHENIC ACID

Pantothenic acid, also known as the filtrate factor, prevents or cures a type of dermatitis peculiar to chickens. In rats, deficiency of this compound causes a dermatitis, intestinal ulceration and also hemorrhagic necrosis in the adrenal cortex.³⁰ There is also evidence that pantothenic acid may be of importance in preventing the graying of hair which occurs in certain laboratory animals suffering from nutritional deficiencies.

Pantothenic acid is present in most animal tissues and in yeast, and recent evidence indicates that it may be a growth-promoting substance of almost universal importance. The pantothenate level of the blood is below normal in pellagra, beriberi, and riboflavinosis.³¹ Signs and symptoms of deficiency in man have not been recognized. The adrenal lesions in experimental animals have suggested a possible relationship of pantothenic acid deficiency to the idiopathic type of Addison's disease (see page 1034).

PARA-AMINOBENZOIC ACID

Para-aminobenzoic acid (PABA) was known as a chemical substance long before its role in

nutrition was suspected. It is now accepted as a member of the B group vitamins. It has been shown recently that it forms a part of the folic acid molecule (see page 416).

There is some evidence that PABA is of more importance than pantothenic acid in preventing the graying of the hair in experimental animals. It has been called the anti-gray hair factor, but evidence that it prevents or cures depigmentation of the hair in man is meager and unsatisfactory.

The physiologic action of PABA is obscure. It is believed to be an essential metabolite for bacteria, and the bacteriostatic action of the sulfonamides is believed to depend on their linkage with and consequent immobilization of an enzyme system which is essential for the metabolism of PABA.³² (This mode of action is known as "competitive inhibition.") No data are available on pure PABA deficiency in experimental animals or in man.

BIOTIN

Biotin (vitamin H, or coenzyme R)³³ is a compound essential for the respiration of certain lower organisms, and probably of all cells. It combines with avidin, a substance present in uncooked egg white, to form a compound which is not absorbed in the intestines. Our present knowledge of biotin deficiency has been gained largely through observations made on animals or human beings who have ingested large amounts of raw egg white. In human volunteers fed a diet in which egg white furnished 30 per cent of total caloric intake, a fine "branny" cutaneous desquamation developed in three or four weeks.³⁴ Later on, anemia, dryness of the skin, lassitude, mental depression, muscle pains, and other symptoms appeared.

CHOLINE

Choline is an important factor in fat metabolism, but its mode of action is not yet entirely clear. It is an essential component of lecithin, a phospholipid which is a constituent of all cells. Lecithin is probably formed in the liver, as a preliminary step in the oxidation of fatty acids.³⁵ Choline deficiency in experimental animals (dogs, rats, and rabbits) particularly when combined with a high intake of fats with saturated fatty acids, reduces the oxidation of fats in the liver, and leads to the accumulation of fat in the liver cord cells, and eventually to cirrhosis.³⁶ In young rats, hemorrhagic cortical necrosis of the kidneys, hemorrhages in other organs, and involution of the thymus are found in addition to fatty livers.³⁷ Cystine-rich diets intensify the liver and kidney lesions while methionine, like choline, reverses the process. Lipocaine, which is obtained by extracting pancreatic tissue, has a similar effect in removing fat accumulation from the liver (lipotropic action). It is a crude extract, containing choline and inositol, as well as some other lipotropic factor which has not been identified.

Considerable interest has developed in the clinical use of choline in early cirrhosis of the liver in man.

INOSITOL

Inositol is a growth stimulant for certain fungi, and is curative for a deficiency disease in mice characterized by retarded growth and loss of hair. It is a constituent of certain phosphatides, and is present in the cephalin fraction of brain and spinal cord tissue.

Like choline, inositol increases the turnover of fat in the liver. Fat accumulation in the liver resulting from biotin administration does not disappear unless lipocaine or inositol is added to the diet.³⁸ Inositol prevents the accumulation of fat in the liver of human beings with cancer of the gastrointestinal tract.³⁹

FOLIC ACID

Folic acid has a molecular weight of about 500, and contains nitrogen but no sulfur or phosphorus. It is apparently identical with a substance essential for the growth of the *Lactobacillus casei* (*L. casei* factor). It is also closely related to vitamin B_c, a crystalline compound isolated from the liver tissue. The *L. casei* factor has recently been synthesized, and it is of interest to note that its molecule contains para-aminobenzoic acid in combination with glutamic acid and a pteridine.⁴⁰

Folic acid deficiency in monkeys causes a nutritional anemia with a reversal in the lymphocyte-neutrophile ratio.⁴¹ Administration of this vitamin to human patients suffering from certain macrocytic anemias, including sprue, macrocytic anemia of childhood, and Addisonian pernicious anemia, causes remissions comparable to those induced by liver therapy.⁴² The exact relationship of folic acid to the extrinsic and intrinsic factors concerned in the etiology of pernicious anemia is not yet clear. The situation is further complicated by the recent isolation from liver tissue of vitamin B₁₂, which also causes remissions in macrocytic anemias, and is believed by many to be the anti-pernicious anemia principle (see page 881).

Vitamin C (Ascorbic Acid)

Chemistry and Physiology.—Ascorbic acid exists in natural source chiefly in the form of L-ascorbic acid. In this form, it readily loses two hydrogen atoms to become dehydroascorbic acid, which is reversibly oxidizable in the body. The physiologic action of vitamin C therefore probably depends on its ability to carry out oxidation-reduction reactions, but the exact part which it plays in cellular physiology has not yet been discovered.

It is clear that ascorbic acid is necessary for the production and maintenance, in certain animals including man and the guinea pig, of

several intercellular substances, notably collagen, osseomucin, chondromucin, dentin, and probably the cement substances which hold vascular endothelial cells together.⁴³ At present we do not know either the normal mechanism of formation of these intercellular materials or the exact role played by ascorbic acid. Collagen apparently is a secretion of the normal fibroblast. Wolbach believes that ascorbic acid is of importance in the late stages of collagen synthesis, and that one of its actions is to change the material from a liquid to a gel state. It is probable that collagen synthesis is an enzymatic reaction, and that vitamin C controls this reaction by a method which is not yet clear.

Under ordinary conditions, fibroblasts in tissue culture do not form collagen, and the addition of ascorbic acid does not lead to collagen formation.⁴⁴ This observation suggests that the mechanism by which ascorbic acid controls collagen deposition is an indirect one, mediated by some endocrine product, or at least by some undiscovered factor.

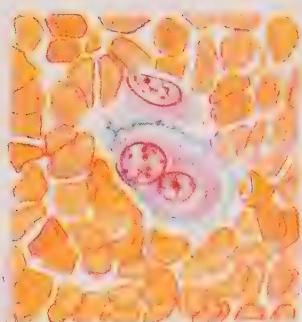
Wound repair in scorbutic guinea pigs was studied by Wolbach.⁴³ The wound fills in normally with blood clot. The clot is then organized by fibroblasts, but without blood vessels. No collagen is formed as long as the scorbutic diet is maintained. With the correction of the deficiency, collagen formation begins within twenty-four hours and proceeds rapidly. The newly formed collagen is for a time homogeneous, but argyrophilic fibers and true collagen fibers soon appear. Fibrin is not changed to collagen, but is liquefied and removed, and the collagen is laid down independently.

Lesions Resulting From Deficiency of Vitamin C.—Essentially similar lesions are found in human beings and in guinea pigs. The outstanding features are (1) hemorrhages and (2) lesions in the skeleton, including the teeth.⁴⁵

Cutaneous hemorrhage, ranging from petechial to massive extravasation, is almost constantly found at autopsy in adults with vitamin C deficiency. The larger hemorrhages correspond to areas of trauma. Hemorrhage into muscles or along fascial planes is seen particularly at points of mechanical stress. Bleeding occurs from capillaries, presumably because of rupture of the loosened endothelial cells. In infants, massive subperiosteal hemorrhage is almost always present, especially

Plate V.—Figures showing the controlled formation of collagen and reticulum in blood clots of guinea pigs rendered scorbutic by deprivation of vitamin C and later recovering with the deposition of intercellular substances owing to the feeding of orange juice. All specimens were fixed in Zenker's fluid and colored with Mallory's connective tissue stain except those of 6 and 8, which were treated by Foot's modification of the Bielschowsky-Maresch silver method before staining. All are $\times 1000$ except figure 8, $\times 430$. 4, Collagen (in blue) being deposited about an isolated cell. Recovery period, seventy-two hours. 5, Slightly more advanced, fibrin strands in red. 6, Fine argyrophilic fibrils (green black) appear; 7, argyrophilic fibrils no longer noticeable. A later stage. Repair ninety-six hours. 8, Argyrophilic fibrils in endochondral bone formation. 9, Endosteal surface of rib in absolute scurbutus. Note fibroblasts and fibroglia fibrils (in red). 10, Similar cells active as osteoblasts in forty-hour recovery period. (Wolbach, courtesy American Journal of Pathology.)

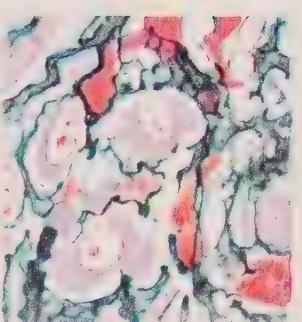
4.



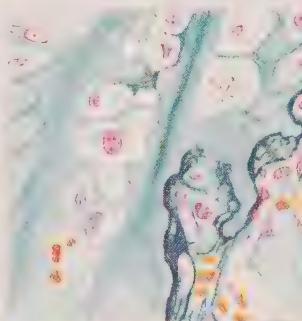
5.



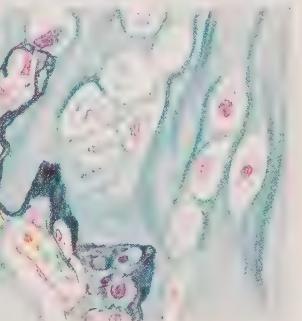
6.



7.



9.



8.



10.

PLATE V. (*For legend see opposite page*).

in the legs. Massive areas of hemorrhage may become infected and suppurate.

Ulceration of the gums, loosening of the teeth, and massive hemorrhage from the gums are commonly seen in adults (Fig. 304) but rarely in infants.

The skeletal lesions, which likewise are due primarily to the failure to produce intercellular substances, are seen most conspicuously at the ends of growing tubular bones. These changes are described in Chapter 42, page 1211.

Death most often results from secondary infection, fatal hemorrhage being a rare cause. Sudden death may follow physical exertion. Fulminating tuberculosis is particularly common. The failure of the normal localization and repair of tubercles by collagenous scar tissue affords a logical explanation of this.

Clinicopathologic Correlation.—The mortality from scurvy is high in untreated cases, but low in recognized cases given adequate therapy.

In infants, pain from subperiosteal hemorrhage is the chief symptom. In general, the symptoms in adults are merely those of general weakness and depression.

Roentgen examination of the bones is an important diagnostic feature in infantile scurvy. Capillary fragility, brought out by means of the tourniquet or other tests, is of some diagnostic value. Chemical determination of the level of ascorbic acid in the blood and urine is also helpful, but in doubtful cases the response to antiscorbutic treatment often gives the best evidence of deficiency. Experienced clinicians feel that mild cases of anorexia and mental depression which are promptly relieved by vitamin C therapy are often caused by deficiency of that vitamin.

Vitamin D

Since the pathologic lesions of vitamin D deficiency are manifested almost entirely in the bones and teeth, this vitamin is discussed in Chapters 25 and 42. For purposes of continuity of thought concerning the vitamins it may be said that vitamin D plays an important role in calcium and phosphorus metabolism. In rickets, the infantile form of vitamin D deficiency, the osteoid tissue in growing bones is not calcified. In the epiphyseal regions, the normally sharp and narrow line of ossification is replaced by a wide and irregular band of uncalcified or poorly calcified osteoid tissue. This results in deformity and bending of the bones near the joints.

In *osteomalacia*, the adult counterpart of rickets, loss of calcium salts and the

accumulation of uncalcified osteoid tissue result in deformities of the pelvic bones and bowing of the long bones.

Hypervitaminosis D.—In experimental animals, very large doses of vitamin D lead to osteoporosis of the skeletal bones, as a result of osteoclastic resorption. Simultaneously there is massive calcium deposition in soft tissues, particularly in the kidneys and arteries. This is referred to as "metastatic calcification." In man, there may be renal damage as a result of calcium deposition.



Fig. 304.—Scurvy, showing gingival swelling and petechiae. (From Mead, Diseases of the Mouth, The C. V. Mosby Co.)

Vitamin E (Alpha-Tocopherol)

Alpha-tocopherol is a complex higher alcohol. Striking effects of deficiency of this vitamin are seen in experimental animals of several species. These effects include cessation of growth, complete sterility in both male and female animals, and great muscular weakness. Microscopically in male animals degeneration of the seminiferous tubular epithelium occurs, resulting in complete aspermatogenesis⁴⁶ (Fig. 305). In female animals the fertilized ova become implanted, but the young embryos become necrotic and are resorbed.⁴⁷ The formation of the fetal placenta is retarded and the maternal-fetal circulation is not properly established. In several species of animals, including guinea pigs and rabbits,⁴⁸ degenerative changes occur in skeletal muscle as a result of vitamin E deficiency. Although the pathologic lesions are similar to those seen in the muscular dystrophies of man, vitamin E has not been found to be of therapeutic value in the latter. There is no conclusive evidence that any of the experimentally produced lesions occur in man as a result of vitamin E deficiency.

In vitamin E-deficient animals, particularly if 20 per cent cod liver oil is present in the diet, an acid-fast lipoid material known as ceroid is found in fat tissue and also in and about many other types of cells.⁴⁹ Apparently

this material represents oxidized fat of the unsaturated type, and one function of vitamin E is believed to be its ability to prevent the oxidation of such fats.

Vitamin K

Vitamin K was named from the Danish word *Koagulation*. It occurs in several closely related forms, its activity apparently being dependent on the component 2 methyl-1,4-naphtho-quinone. Although fat soluble, certain active compounds which are water soluble can be prepared. This vitamin was discovered by Dam in 1935 as a result of careful study of a hemorrhagic disease which he observed in chickens.⁵⁰ It was later isolated by Doisy and his co-workers.⁵¹ Physiologically, it is necessary for the formation of prothrombin, so that in its absence the mechanism of blood coagulation breaks down.

portance in the solution of the cancer problem. Vitamins, particularly those of the B group, are intimately concerned with the physiology of all living cells. For these reasons, various investigators have studied the vitamin requirements and the vitamin content of malignant and normal tissues.⁵³ One obvious possibility would be the discovery of a vitamin which was so much more essential for malignant than for normal cells that depletion of that vitamin would cause regression of the tumor.

In one special type of tumor, this has been accomplished. A carcinoma of the liver (hepatoma) produced in rats by feeding a dye known as "butter yellow," is prevented, under certain conditions, by biotin deficiency.⁵⁴ Dietary relationships in this tumor are quite complex. Yeast, liver, whole B complex, and a combination of riboflavin and casein all counteract the carcinogenic action of butter yellow, perhaps by



Fig. 305.—A seminiferous tubule from a rat fed a diet deficient in vitamin E. The cells have atrophied and desquamated. The crescentic chromatin masses and huge, multinucleated cells are typical of advanced vitamin E deficiency. (From Eddy and Dalldorf, *The Avitaminoses*, Williams and Wilkins Co.)

Clinically, vitamin K is of great importance in preventing hemorrhagic disease of the newborn.⁵² In adults, simple deficiency is of rare occurrence, because of the abundance of this vitamin in leafy vegetables and other common foods and because of its formation by intestinal bacteria. Conditioned deficiency occurs frequently in obstructive jaundice, since vitamin K is not absorbed satisfactorily in the absence of bile from the intestine. In the presence of liver damage, administration of vitamin K is usually ineffective in preventing hemorrhage.

Vitamins and Cancer

An understanding of the metabolic peculiarities of malignant cells is of fundamental im-

helping the liver cells to detoxify the dye. Pyridoxine, like biotin, definitely favors the production of hepatomas in rats fed butter yellow.

The vitamin content of several types of malignant tissue has been shown to form a pattern unlike that of any normal tissue.⁵³ Specifically, in human cancer tissue inositol and folic acid are present at much higher levels while biotin, pyridoxine, and riboflavin are present at much lower levels than those found in normal tissues. Pantothenic acid, niacin, and thiamine were found to be moderately reduced in human cancer tissue.

The ability of certain folic acid analogues to cause temporary remissions in cases of acute leukemia has been mentioned.

Vitamins and Infection

Many vitamins, especially those of the B group, are as important for bacterial metabolism as they are for higher forms of life. Para-aminobenzoic acid apparently is an essential metabolite for many bacteria, and the sulfonamides are believed to act by linking with an unknown enzyme system in such a way that PABA cannot be utilized by the bacteria.

It has been stated previously that the bacterial complications occurring in vitamin A deficiency may be explained largely on a mechanical basis. Reduced resistance to tuberculosis and to salmonella infection in vitamin A-deficient animals has been reported, but the specific role of vitamin A in maintaining resistance to bacterial infection needs further study.

The importance of vitamin C in tuberculosis has been discussed above. Several reports indicate that C-deficient animals show greater morbidity and mortality from a variety of bacterial infections than controls on a normal diet. The reasons for this are not yet clear. The possible role of ascorbic acid and other vitamins in antibody formation is under investigation, but conflicting results have been reported.

In the case of obligate intracellular parasites, whose metabolism is intimately related to that of the cells in which they grow, several observations of importance have been made. Riboflavin deficiency specifically lowers the resistance of rats to infection by typhus rickettsiae, undoubtedly because it asphyxiates the cells by paralyzing cellular respiration.⁵⁵ Similarly, thiamine deficiency greatly lowers resistance to psittacosis,⁵⁶ and also to rat leprosy.⁵⁷

Para-aminobenzoic acid exerts a striking therapeutic effect in experimental murine typhus infection.^{58, 59} The mechanism of this action has not yet been established, but a marked increase in the rate of intracellular metabolism may be an important factor.⁶⁰

Certain smaller viruses, such as that of poliomyelitis, however, are inhibited under certain conditions by riboflavin or by thiamine deficiency, suggesting that they thrive better when their host cells are metabolizing normally. The theory that alterations in cellular metabolism brought about by variations in dietary factors may modify the course of infections caused by bacteria, viruses, and protozoa is supported by an increasing body of experimental evidence.⁶¹

Lesions Resulting From Starvation

In human beings maintained on a low caloric intake, certain lesions develop quite independently of the changes caused by specific dietary deficiencies. In studying the post-mortem material from prison camps in World War II, the author found only the changes of inanition. No evidence of viral infection was found, but there was a high incidence of fulminating pulmonary tuberculosis, which often would have been regarded as pyogenic pneumonia if acid-fast stains had not been made.

The changes of inanition include great loss of weight, serous atrophy of fat throughout the

body, and marked reduction in the amount of lymphoid tissue.⁶² Atrophy of the testes and ovaries, with absence of spermatogenesis and ovogenesis is invariably noted. Both cardiac and skeletal muscle cells become so small that they are recognized with difficulty. The liver cord cells also become small and the weight of the liver may be reduced by 50 per cent or more. Hemosiderosis of the spleen is a constant finding, and the adrenals show lipoid depletion. In children there is cessation of bone growth.

Specific Amino Acid Deficiencies

In rats and dogs, ten of the amino acids are indispensable for normal growth: tryptophane, lysine, histidine, arginine, phenylalanine, isoleucine, leucine, threonine, methionine, and valine.⁶³ With the exception of arginine and histidine, these are all essential to produce a positive nitrogen balance in man. A few specific lesions have been described in animals as a result of deficiency of these elements; for example, tryptophane deficiency in rats causes, in addition to cessation of growth, alopecia, cataract, anemia, and hypoproteinemia. Valine deficiency in rats causes sensitivity to touch and a spinning motion, while in the dog valine is necessary for plasma protein and hemoglobin formation. Lysine deficiency in man causes nausea, dizziness, and hypersensitivity to metallic sounds, while certain unidentified non-ketonic organic acids appear in the urine.⁶⁴ In general, changes due to specific amino acid deficiencies are unlikely to occur in man except under experimental conditions, and our information on the entire subject is meager.

Specific Fatty Acid Deficiency

Linoleic acid deficiency in rats causes scaling of the skin, alopecia, and injury to renal and testicular tubular epithelium. There is at present little evidence for the occurrence of essential fatty acid deficiency in man.

The Essential Elements

In addition to carbon, hydrogen, oxygen, and nitrogen, fourteen other elements are considered essential for life; namely, calcium, magnesium, potassium, sodium, sulfur, phosphorus, chlorine, iron, copper, cobalt, manganese, zinc, iodine, and probably fluorine. Many other elements are, however, present in tissues and studies of their possible importance are far from complete. In addition to the more obvious functions of calcium, magnesium, phosphorus, sodium, and chlorine in acting as structural components and in maintaining the acid-base equilibrium, it has been shown that traces of several metallic elements, such as zinc, copper, manganese, and magnesium, are of vital importance, since they form essential components of certain enzyme systems.^{65, 66, 67, 68} The function of iron as a component of hemoglobin and of intracellular oxidizing enzymes is too well known to require comment. Iron-deficiency anemia is discussed elsewhere.

Calcium is important for the contraction of heart muscle and for blood coagulation. Its im-

portance is rickets and osteomalacia and its relation to the parathyroids are discussed elsewhere.

Magnesium deficiency in rats causes dilatation of cutaneous vessels, hyperirritability, and tetanic convulsions.⁶⁹ The paws become edematous and ulcerated. In the kidneys degeneration of the tubules and glomeruli, with calcium deposition, has been described.⁷⁰ In the teeth, there is atrophy of the odontoblasts and ameloblasts, with retardation of dentine and enamel formation.

Potassium deficiency in experimental animals causes necrosis of myocardial fibers and renal tubules.^{71, 72} In man, potassium deficiency occurs as a result of the injection of desoxycorticosterone, and in dehydrated infants, as well as in familial periodic paralysis. Electrocardiographic changes are occasionally seen in such patients when the blood potassium level is lowered.

Sodium deficiency in rats causes vascularization of the cornea and squamous metaplasia of epithelium, with obstruction of the tarsal glands. It has been shown⁷³ that a low sodium diet decreases the blood glutathione level and causes increased susceptibility to the diabetogenic action of alloxan. Nothing is known concerning sodium deficiency in man except in connection with concomitant chloride deficiency. The electrolyte imbalance which occurs in shock, Addison's disease, rickettsial diseases, and in other conditions is considered elsewhere.

Sulfur is extremely important physiologically, but it would be difficult to produce inorganic sulfur deficiency because while this element occurs in methionine and cystine, inorganic sulfur cannot be used in the formation of these compounds.⁷⁴ Sulfur is most important in the sulfhydryl (-SH) form in which state it is an active component of many enzymes, vitamins, and hormones. Oxidation of this group to the inactive (S-S) form is believed to be the mechanism of action of many enzyme inhibitors, such as diabetogenic alloxan⁷⁵ and certain carcinogenic hydrocarbons. It should be noted, however, that insulin is an exception to the rule since it is active only when its sulfur is in oxidized form.

Phosphorus deficiency is known only in connection with the complex situation which develops in vitamin D deficiency.

Chloride deficiency is difficult to study in an isolated form, but in rats apparently leads to the formation of alkaline urine, with the precipitation of calcium in the renal tubules.⁷⁶ Gastric tetany in man, resulting from pyloric obstruction, probably represents pure chloride deficiency and has been relieved by giving chlorides.

Copper is important in hematopoiesis, and is an essential constituent of several important enzymes. Experimental deficiency in the rat, for example,⁷⁷ leads to a microcytic hypochromic anemia, and the rats often die before the anemia becomes severe. Deficiency of this element also causes graying of the hair, which is not prevented by large amounts of pantothenic acid or para-aminobenzoic acid (the other "antigray-hair" factors).⁷⁸ A paralytic disease

in lambs known as "swayback" is apparently due to copper deficiency.⁷⁹ Pathologically, in this condition, one finds symmetric diffuse demyelination and softening of the white matter of the brain, giving a picture resembling that of Schilder's disease in man. Nothing is known concerning copper deficiency in man.

Cobalt deficiency in sheep and cattle is accepted as the cause of a severe anemia with hemosiderosis of the spleen.⁸⁰ Deficiency of this element in man has not been recognized, but it is a component of vitamin B₁₂, which is believed to be the antipernicious anemia principle present in liver.

Manganese deficiency has been largely neglected from the histologic viewpoint. In experimental animals disturbance of growth occurs in the offspring of deficient mothers, with frequent death and osseous defects in surviving animals.⁸¹ Lesions in the human being are unknown.

Zinc is an important component of carbonic anhydrase, uricase, insulin, and phosphatase. Dietary deficiency in rats causes corneal vascularization, alopecia, keratinization of the skin and esophagus, and death in a few weeks.⁸² Deficiency in man probably does not occur.

Iodine deficiency is related to lesions of the thyroid gland, and is discussed under that heading.

Fluorine inactivates phosphatase and several other enzyme systems. Experimental fluorine deficiency in rats has been reported to cause dental caries.⁸³ For a discussion of the effects of fluorine on teeth and bones, see pages 156 and 1191.

References

- General*
- Eddy, Walter H., and Dalldorf, Gilbert: *The Avitaminoses*, ed. 3, Baltimore, 1944, Williams & Wilkins Co.
 - Wolbach, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies, *Physiol. Rev.* **22**: 233, 1942.
 - Rosenberg, H. R.: *Chemistry and Physiology of the Vitamins*, New York, 1942, Interscience Publishers.
 - Follis, R. H., Jr.: *The Pathology of Nutritional Disease*, Springfield, Ill., 1948, Charles C Thomas.

• Physiology

- 1. The Biological Action of the Vitamins. A Symposium edited by E. A. Evans, Jr., 1942, University of Chicago Press.
- 2. Green, D. E.: Advances in Enzymology **1**: 177, 1941 (enzymes and trace substances).
- 3. Beadle, G. W.: Am. Scientist **34**: 31, 1946 (genes and the chemistry of the organism).
- 4. Zweifach, B. W., Black, M. M., and Schorr, E.: Proc. Soc. Exper. Biol. & Med. **74**: 848, 1950.
- 5. Dempsey, E. W., and Wisloki, G. B.: Physiol. Rev. **26**: 1, 1946 (histochemical contributions to physiology).
- 6. Wolbach, S. B.: Science **86**: 569, 1937.
- 7. Farber, S.: New England J. Med. **238**: 787, 1948.
- 8. Evans, C. A., Carlson, W. E., and Green, R. G.: Am. J. Path. **18**: 79, 1942.

Vitamin A

- 9. Popper, H.: Arch. Path. **31**: 766, 1941 (histologic distribution of vitamin A).
- 10. Wolbach, S. B.: Proc. Inst. Med. Chicago **16**: 119, 1946 (vitamin A in relation to skeletal growth). ♀

11. Wolbach, S. B., and Bessey, O. A.: Arch. Path. 32: 689, 1941 (vitamin A deficiency and the nervous system).
 12. Boyle, P. E.: J. Dent. Research 13: 39, 1933.

Thiamine

13. Weiss, S.: J. A. M. A. 115: 832, 1940 (occidental beriberi).
 14. Swank, R. L., and Bessey, O. A.: J. Nutrition 22: 77, 1941 (avian thiamine deficiency).
 15. Street, H. R., Zimmerman, H. M., Cowgill, G. R., Hoff, H. E., and Fox, J. C.: Yale J. Biol. & Med. 13: 293, 1941.
 16. Alexander, L.: Am. J. Path. 16: 61, 1940 (Wernicke's disease).
 17. Williams, R. R., and Spies, T. D.: Vitamin B₁ (Thiamine) and Its Use in Medicine, New York, 1938, The Macmillan Co.

Niacin

18. Warburg, O., and Christian, W.: Biochem. Ztschr. 285: 156, 1936 (physiologic action).
 19. Spies, T. D., Bean, W. B., and Ashe, W. F.: Ann. Int. Med. 12: 1830, 1938.
 20. Woolley, D. W.: J. Biol. Chem. 163: 773, 1946.
 21. Moore, R. A., Spies, T. D., and Cooper, Z. K.: Arch. Dermat. & Syph. 46: 100, 1942 (skin in pellagra).
 22. Denton, J. A.: Am. J. Path. 4: 341, 1928 (pellagra).
 23. Arton, S. T., and Bender, L.: Bull. Neurol. Inst. New York 1: 506, 1931.

Riboflavin

24. Bessey, O. A., and Wolbach, S. B.: J. Exper. Med. 69: 1, 1939.
 25. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D.: J. A. M. A. 114: 2437, 1940.
 26. Spies, T. D.: Riboflavin Deficiency. In Cecil's Text Book of Medicine, Philadelphia and London, 1947, W. B. Saunders Co.
 27. Warkany, J., and Schrannberger, E.: J. Nutrition 27: 477, 1944.

Pyridoxine

28. Györgyi, P.: Biochem. J. 29: 741, 1935.
 29. Spies, T. D., Bean, W. B., and Ashe, W. F.: J. A. M. A. 112: 2414, 1939.

Pantothenic Acid

30. Daft, F. S., Sebrell, W. H., Babcock, S. H., and Jukes, T. H.: Pub. Health Rep. 55: 1333, 1940.
 31. Spies, T. D., Stanberg, S. R., Williams, R. J., Jukes, T. H., and Babcock, S. H.: J. A. M. A. 115: 523, 1940 (importance in man).

Para-aminobenzoic Acid

32. Wood, W. B., Jr.: J. Exper. Med. 75: 369, 1942.

Biotin

33. Györgyi, P., Melville, D. B., Burk, D., and Du Vigneaud, V.: Science 91: 243, 1940.
 34. Sydenstricker, V. P., Singal, S. A., Briggs, A. P., Devaughn, N. M., and Isbell, H.: J. A. M. A. 118: 1199, 1942.

Choline

35. Griffith, W. H.: J. Nutrition 22: 239, 1941.
 36. Bloomberg, E., and McCollom, E. V.: Science 93: 598, 1941.
 37. Christensen, K.: Arch. Path. 34: 633, 1942.

Inositol

38. Gavin, G., Patterson, J. M., and McHenry, E. W.: J. Biol. Chem. 148: 275, 1943.
 39. Abels, J. C., Kupel, C. W., Pack, G. T., and Rhoads, C. P.: Proc. Soc. Exper. Biol. & Med. 54: 157, 1943.

Folic Acid

40. Angier, R. B., Cosulich, D. B., and others: Science 103: 667, 1946.
 41. Cooperman, J. M., Elvehjem, C. A., McCall, K. B., and Ruegamer, W. R.: Proc. Soc. Exper. Biol. & Med. 61: 92, 1946.
 42. Spies, T. D.: J. A. M. A. 130: 474, 1946.

Vitamin C

43. Wolbach, S. B.: Am. J. Path. 9: 689, 1933.
 44. Hass, G. M., and McDonald, F.: Am. J. Path. 16: 525, 1940.
 45. Dalldorf, G.: J. A. M. A. 111: 1376, 1938.

Vitamin E

46. Mason, K. E.: Am. J. Anat. 52: 153, 1933.
 47. Evans, H. M., and Burr, G. O.: Memoir, Univ. of California 8: 1, 1927.
 48. Goettsch, M., and Pappenheimer, A. M.: J. Exper. Med. 54: 145, 1931.
 49. Maser, K. E., Dam, H., and Granados, H.: Anat. Rec. 94: 265, 1946.

Vitamin K

50. Dam, H., and Schonheyder, F.: Biochem. J. 28: 1355, 1935.
 51. McKee, R., Binkley, S. B., Thayer, S. A., MacCorquodale, D. W., and Doisy, E. A.: J. Biol. Chem. 131: 327, 1939.
 52. Waddell, W. W., Jr., and Lawson, G. McL.: J. A. M. A. 115: 1416, 1940.

Vitamins and Cancer

53. Williams, R. J.: B Vitamins and Cancer, In A. A. A. S. Research Conference on Cancer, A. A. A. S., Washington, D. C.
 54. du Vigneaud, V., Spangler, J. M., Burk, D., Kensler, C. J., Sugiura, K., and Rhoads, C. P.: Science 95: 174, 1941.

Vitamins and Infection

55. Pinkerton, H., and Bessey, O. A.: Science 89: 368, 1939.
 56. Pinkerton, H., and Swank, R. L.: Proc. Soc. Exper. Biol. & Med. 45: 704, 1940.
 57. Lamb, A. R.: Am. J. Hyg. 21: 438, 1935.
 58. Snyder, J. C., Maier, J., and Anderson, C. R.: Confidential Report to National Research Council, 1942.
 59. Greiff, D., Pinkerton, H., and Moragues, V.: J. Exper. Med. 80: 561, 1944.
 60. Greiff, D., and Pinkerton, H.: J. Exper. Med. 87: 175, 1948.
 61. Clark, P. F., McClung, L. S., Pinkerton, H., Price, W. H., Schneider, H. A., and Trager, W.: Bact. Rev. 13: 99, 1949 (symposium on influence of nutrition in infection).

Starvation

62. Jackson, C. M.: The Effects of Inanition and Malnutrition Upon Growth and Structure, Philadelphia 1925, P. Blakiston's Sons and Co.

Amino Acid Deficiency

63. Rose, W. C.: Physiol. Rev. 18: 109, 1938 (general discussion).
 64. Albanese, A. A., and others: Proc. Soc. Exper. Biol. & Med. 52: 209, 1943 (lysine deficiency in man).

Essential Elements

65. Keilin, D., and Mann, T.: Nature 144: 442, 1939.
 66. Keilin, D., and Mann, T.: Proc. Nut. Soc. Camb. 1: 189, 1944.
 67. Richards, M. M., and Heilerman, L.: J. Biol. Chem. 134: 237, 1940.
 68. Banga, I., Ochoa, S., and Peters, R. A.: Biochem. J. 38: 1980, 1939.

69. Kruse, H. D., Orent, E., and McCollom, E. V.: *J. Biol. Chem.* **96**: 519, 1932.
70. Sullivan, M., and Evans, V. J.: *J. Nutrition* **27**: 123, 1944.
71. Liebow, A. A., McFarland, W. J., and Tennant, R.: *Yale J. Biol. & Med.* **13**: 523, 1941.
72. Follis, R. H., Jr., Orent-Keiles, E., and McCollom, E. V.: *An. J. Path.* **18**: 29, 1942.
73. Grunert, R. R., and Phillips, P. H.: *J. Biol. Chem.* **181**: 821, 1949.
74. Tarver, H., and Schmidt, C. L. A.: *J. Biol. Chem.* **146**: 69, 1942.
75. Lazarow, A.: *Proc. Soc. Exper. Biol. & Med.* **61**: 441, 1946.
76. Lowenkaupt, E., and Greenberg, D. M.: *Arch. Path.* **42**: 49, 1946.
77. Smith, S. E., Medlicott, M., and Ellis, G. H.: *Am. J. Physiol.* **142**: 179, 1944.
78. Keil, H. L., and Nelson, V. W.: *J. Biol. Chem.* **93**: 49, 1931.
79. Innes, J. R. M., and Shearer, G. D.: *J. Comp. Path.* **53**: 1, 1940.
80. Moore, H. O.: *Bull. Coun. Sci. Ind. Res. Aust.* **113**: 86, 1938.
81. Barnes, L. L., Sperling, G., and Maynard, L. A.: *Proc. Soc. Exper. Biol. & Med.* **46**: 562, 1941.
82. Day, H. G., and McCollom, E. V.: *Proc. Soc. Exper. Biol. & Med.* **45**: 282, 1940.
83. McClendon, J. F., and Foster, W. C.: *Fed. Proc.* **4**: 159, 1945.

Chapter 18

NEOPLASMS

SHIELDS WARREN

A neoplasm is an uncontrolled new growth of tissue. Attempts to improve on this basic definition given by Ewing have been only confusing. The term "tumor" is properly applied to any neoplasm, benign or malignant. Tumors or tumorlike growths occur in most vertebrates, some insects and plants. Probably they will be found in all multicellular organisms as we become better able to recognize them in the less complex forms. Their occurrence in other forms than man has been most helpful in studying their genesis and behavior.

General Characteristics

The cells of a tumor are permanently altered cells of the body which have the power of growth and multiplication relatively free from the usual restraints of the body. They are not anarchic. These cells, however, in general have certain characteristics in common, though there is no more resemblance between the cells of a carcinoma of the rat and a carcinoma of man than there is between hepatic cells of the rat and hepatic cells of man. The cells of a tumor usually resemble sufficiently the parent tissue from which they have been derived to enable them to be identified. Some of them are sufficiently highly specialized to produce characteristic secretions such as melanin, osteoid, insulin, or parathyroid hormone. The consistency of the cell pattern of a given tumor is illustrated by some of the transplantable tumors (Fig. 306) which have retained their characteristics through repeated animal transfers over many years.

The cells of a malignant tumor are usually less differentiated than those of the normal tissue in which they took origin, and may show striking variations in size, shape, and texture. The cells of a benign tumor, however, closely resemble

those of the parent tissue, and may well be indistinguishable from normal cells except for their arrangement and growth potential.

A tumor consists of two parts—the tumor cells proper and their supporting framework of connective tissue and vascular supply, the stroma (Fig. 307). The stroma is derived from the normal tissues of the host. The amount and vascularity of the stroma vary greatly. In general, rapidly growing tumors, particularly sarcomas, have a highly vascular stroma with little connective tissue. More slowly growing tumors are less well vascularized, and in some, such as scirrhous carcinomas of the breast, most of the tumor mass consists of dense connective tissue.

Tumors cannot grow in the body to any extent without stroma, with the exception of leukemia and some that thrive in transudates into body cavities.

While nerves may be present in tumors as result of survival during infiltration of pre-existing structures, and while nerve filaments may be formed, chiefly in relation to stromal vessels, tumors are not under nervous control. Some tumors actually have neurons as components, but appear to be nonfunctioning. Until tumors are large enough to impinge on pre-existing sensory nerves, pain does not result.

A cancer is a malignant neoplasm. Cancer is also applied generally to the syndrome associated with the development of a malignant tumor. From the clinical standpoint, cancer is not one disease, but many. A basal-cell carcinoma may be present many years before it kills and remain localized throughout its course (Fig. 308); a carcinoma of the breast (Fig. 309) may develop, spread widely, and kill in a few months.

Carcinoma is a malignant tumor of epithelial tissue, sarcoma one of mesen-

chymal tissue. A teratoma is a tumor reproducing ectodermal, entodermal, and mesenchymal tissues and may be either benign or malignant.

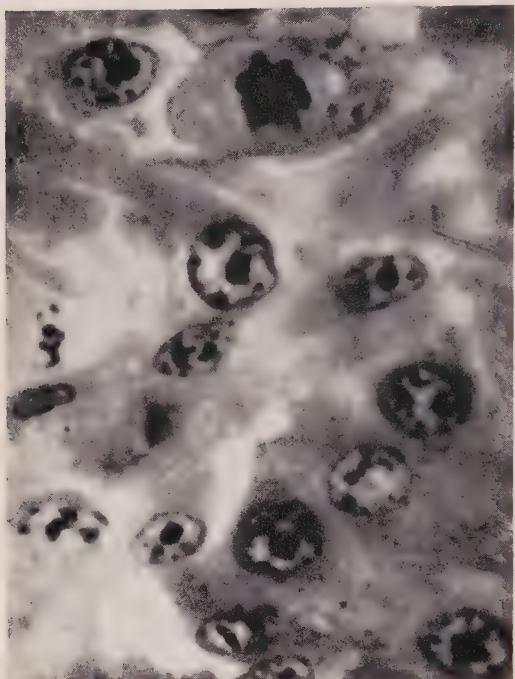


Fig. 306.—A high-power view of Walker rat carcinoma No. 256. ($\times 1,350$.)

Differentiation of Benign and Malignant Tumors

A benign tumor usually presents itself as a gradually increasing swelling (Fig. 310); a malignant tumor as either a swelling or an ulcer with raised edges.

Malignant tumors have four general characteristics that differentiate them from benign tumors. So far as the evidence available at present is concerned, once a cell becomes malignant it does not revert to normal.

Malignant tumors tend to be anaplastic—that is, to be less differentiated than the normal cells from which they are derived. This leads to a resemblance to more embryonic forms of cells, and the rather too extreme statement has been made that “oncogeny is a recapitulation of ontogeny.”

Malignant tumors infiltrate and destroy adjacent normal tissue, whereas benign tumors grow by expansion and merely

push aside normal tissue. Consequently the outlines of a malignant tumor are usually irregular and vague, whereas those of a benign tumor are usually rounded and often surrounded by a capsule. This capsule is largely fibrous tissue persisting from dislodged normal tissue, but in part is new-formed fibrous tissue.

Malignant tumors in general are more rapid growing, increasing perceptibly during weeks or months; benign tumors are slow growing, often requiring years to attain a large size. This difference in rate of growth is apparent on microscopic examination also. Mitotic figures and young cells may be relatively frequent in a cancer, while they are rare in a benign tumor and in most normal tissues. Twenty or more mitoses per 1,000 cells is not an unusual proportion in a malignant tumor (Fig. 311), whereas under one per thousand is usual in benign tumors or normal

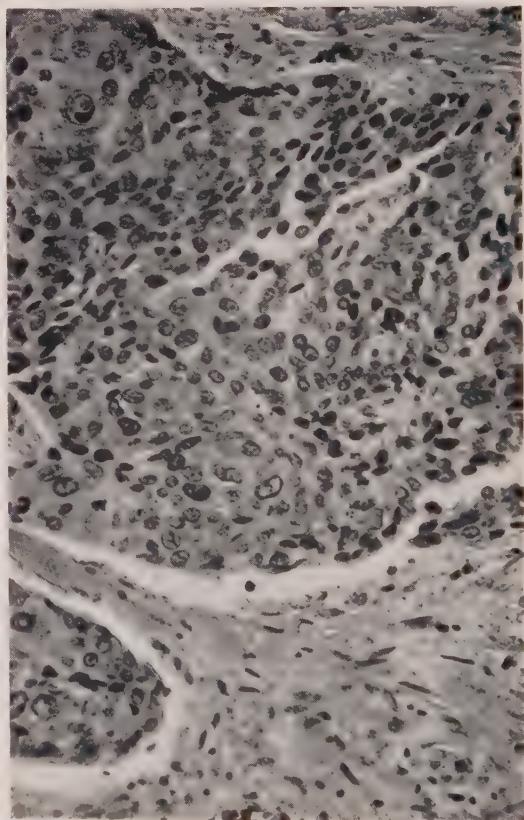


Fig. 307.—Epidermoid carcinoma of the bladder showing the masses of tumor cells and the supporting connective tissue stroma with its blood vascular channels. Woman, 73 years of age. ($\times 235$.)



Fig. 308.—A slowly growing, localized, basal-cell carcinoma of the skin. Twenty years' duration. Man aged 58 years. These localized cancers, unless adequately treated, may be widely destructive.



Fig. 309.—Advanced fungating carcinoma of the breast. Woman 47 years of age. Six months' duration.

tissue. Rapidity of growth in itself is not an indication of a malignant tumor, nor is the presence of mitotic figures such an indication. Abnormal mitoses are much more frequent in malignant tumors than in other tissues, but again are not pathognomonic (Fig. 312). Such mitoses may result in the formation of tumor giant cells, others result in cells that die rapidly.



Fig. 310.—Subcutaneous lipoma which had gradually increased in size over a period of years. Note the stretching of the skin as evidenced by the widely separated pores. Man, 70 years of age. Six to eight years' duration.

The mitotic rate would lead one to expect more rapid growth of cancer than occurs. The lag is due to such factors as production of some nonviable cells, desquamation of superficial cells when ulceration occurs, necrosis from inadequate stromal blood supply, and necrosis caused by secondary bacterial infection.

Many attempts have been made to diagnose the presence and character of a tumor by study of single component cells.

All suggested methods are fraught with difficulty, and most are none too accurate. The most successful method of recognizing the cells of malignant tumors is that developed by Papanicolaou. By making smears from bodily secretions and by studying the cells contained in them, he has been able to devise practical diagnostic procedures with a fairly high degree of accuracy in case of malignant tumors of the female genital tract (Fig. 313), of the bladder, of the bronchus, and in serous exudates.

The general cytological characteristics of malignant cells as seen in these smears may be summarized as follows. Malignant cells vary more in size and shape than do those of normal tissue. The nucleus is usually hyperchromatic and the ratio of the nuclear mass to cytoplasm is relatively high. Nucleoli are apt to be more prominent than they are in normal cells of corresponding tissues. Vacuolization is a much more frequent occurrence in both cytoplasm and nucleus of malignant tissue than in normal tissue. Abnormalities of mitosis are much more fre-

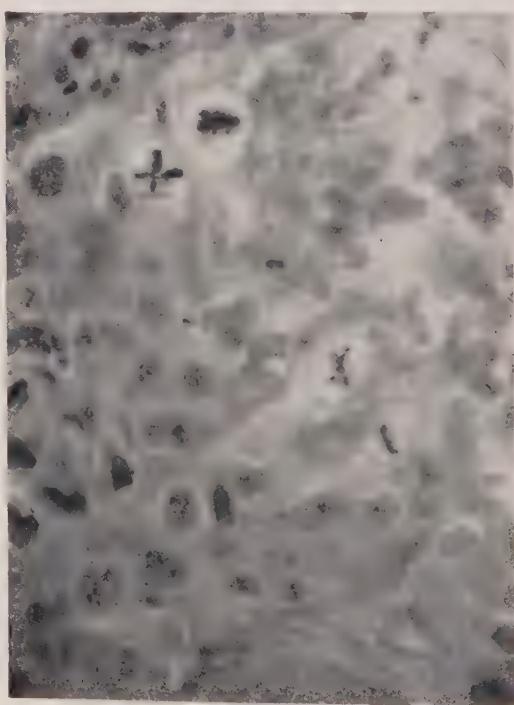


Fig. 311.—Numerous mitoses in the cells of an epidermoid carcinoma, Grade III, of the rectum. ($\times 500$.)

quent in malignant tissues than in normal tissue, but they are not pathognomonic of malignancy.

Malignant tumors have the power of metastasis, and to this power is due much of their menace. This establishment of secondary deposits at a distance is a major factor in the lethal character of the disease, and one of the chief obstacles to its successful treatment. Benign tumors remain localized and do not metastasize.

Incidence and General Aspects of Race, Sex, and Age

There is no one of the higher animals from fish to man (Figs. 315 and 316) that has been carefully studied in which tumors do not occur. The statement that cancer is a disease of civilization, that it does not occur in one or another of the primitive races, has had to be corrected as our knowledge of these primitive races has increased.

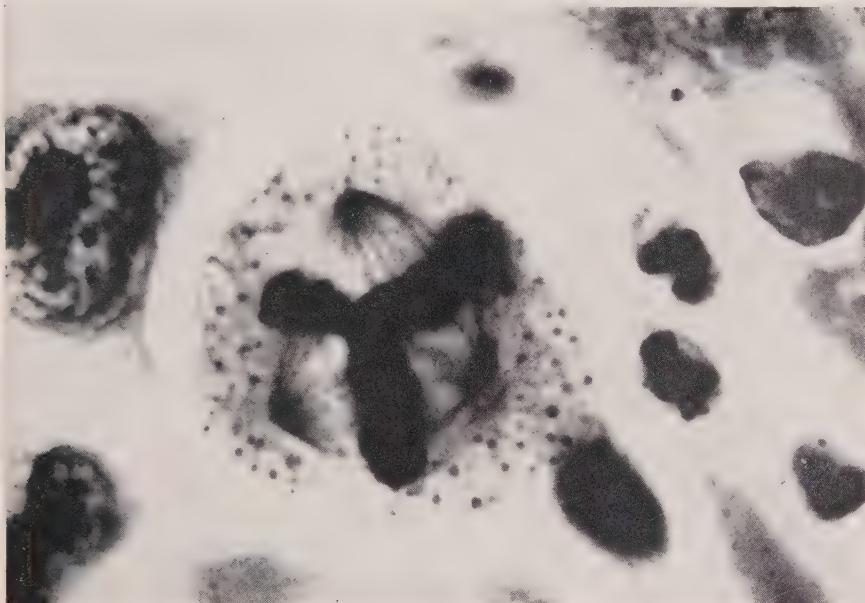


Fig. 312.—An abnormal tripolar mitosis occurring in a malignant melanoma. Phosphotungstic acid-hematoxylin stain. ($\times 2,350$)

No one criterion of malignancy is absolute in itself. At least two are needed to establish the diagnosis of malignancy. Thus, cytologic abnormalities in cells such as hyperchromatism, abnormal mitosis, and variation in size may result from cellular injury by radiant energy, by cold, by heat, by certain types of narcotics. Invasive growth including invasion of blood vessels is normal in the placenta. Metastasis occurs in endometriosis.

No characteristic chemical substance has been derived from tumor cells. While there are some differences in metabolism, particularly the anaerobic metabolism of tumor cells and normal cells, these are not constant and are not sufficiently characteristic to be of diagnostic value.

While there is apparently no age and no race in which tumors will not appear, there are certain general predilections which are of much interest and which, when better understood, may throw some light on the etiology. In general, malignant tumors tend to occur in the older age groups and the percentage of increase rises rapidly with age, as indicated by Fig. 314. The cancer death rate in a population such as ours tends to be about 130 per 100,000. Since the average duration of a case with malignant tumor is about three years, the prevalence rate is about 400 per 100,000. No figures of value exist for the frequency of benign tumors.

Certain specific types of tumors will occur predominantly at well-defined

periods. Thus, leiomyomas of the uterus almost always are noted in women between 35 and 45 years of age. Sex differences in some tumors are quite striking. Thus, cancer of the lower lip is an extreme rarity in women, but not infrequent in men (Fig. 317). Cancer of the skin of the ear occurs ten times as frequently in men as in women. Cancer of the thyroid occurs seven times as frequently in women as in men.

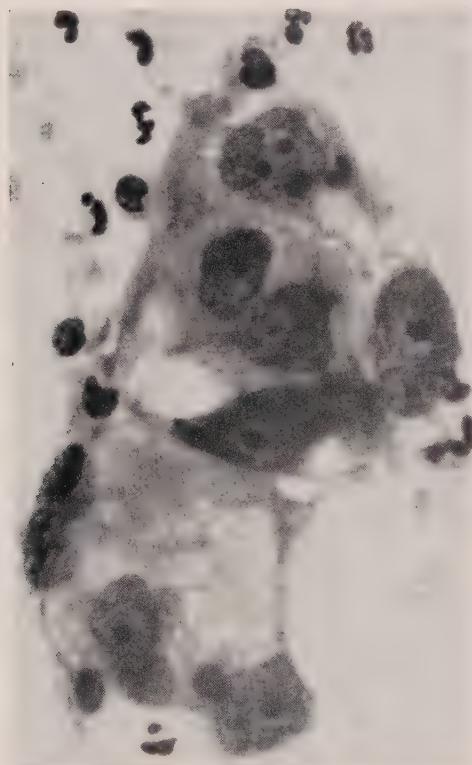


Fig. 313.—Malignant cells in vaginal secretion prepared by the Papanicolaou technique. Note the abnormal size and shape of the cells, the density of chromatin in the nuclei, and the prominent nucleoli. Numerous polymorphonuclear leukocytes are also present. ($\times 650$)

Racial differences are quite striking on basis of statistics as available at the present time. However, it is possible that advancement in our knowledge will alter the picture. Cancer of the breast is one of the most frequent neoplasms in American women, and it is rare among Japanese women. Cancer of the liver is essentially rare among Americans and Europeans, but is fairly frequent among Orientals. Epidermoid and basal-cell

carcinomas of the skin are very common in the white race, but very rare in the Negro.

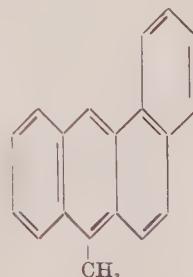
Cancer is rare among young persons and strikingly common among older people. The progress of the disease is often much more rapid among young persons than in the very old. An acute leukemia in childhood may kill in a few weeks, whereas a carcinoma of the prostate in an 80-year-old man may run a slow course of many years, even untreated.

Etiology

There is no one cause for the development of tumors. Some factors in the production of tumors both in animals and man are established, others are unknown. Tumors are not restricted to man, but they occur throughout groups of vertebrates, and analogues to them exist among other forms of life.

Cocarcinogenic activity—a synergistic effect by which two or more carcinogenic agents, each in subliminal amount, will combine to produce a cancer—indicates that certain general cell changes must occur as cancer develops.

Chemical Carcinogens.—The first hint that there might be specific causes for cancer was found by Sir Percival Pott, who noted that the chimney sweeps in London had far more carcinomas of the scrotum than occurred in the general population. As a result of this observation, there was continued interest in soot and coal tar as a possible stimulus for the development of tumor, which eventually led to the first experimental production of tumors by Yamagawa and Ichikawa through painting repeatedly the ears of rabbits with coal tar. This was followed by the discovery by Cook and Kennaway that specific hydrocarbons of the benzanthracene group could produce sarcomas or carcinomas when brought into contact with the appropriate tissues of mice. A wide variety of carcinogenic compounds have now been discovered. An example of the structural formula of 10-methyl-1,2-benzanthracene, one of the more active compounds, follows:



10-Methyl-1,2-Benzanthracene

In man, prolonged exposure to coal tar or to certain types of oil (Fig. 318) has been shown to be carcinogenic. Likewise, naphthylamine has been proved to produce papillomas and carcinomas of the bladder in man.

tested out on rodents have proved to be without carcinogenic effect in the case of primates.

Some carcinogens are effective when ingested. Feeding mice with the dye, butter yellow, produces cancer of the liver. If the animals are

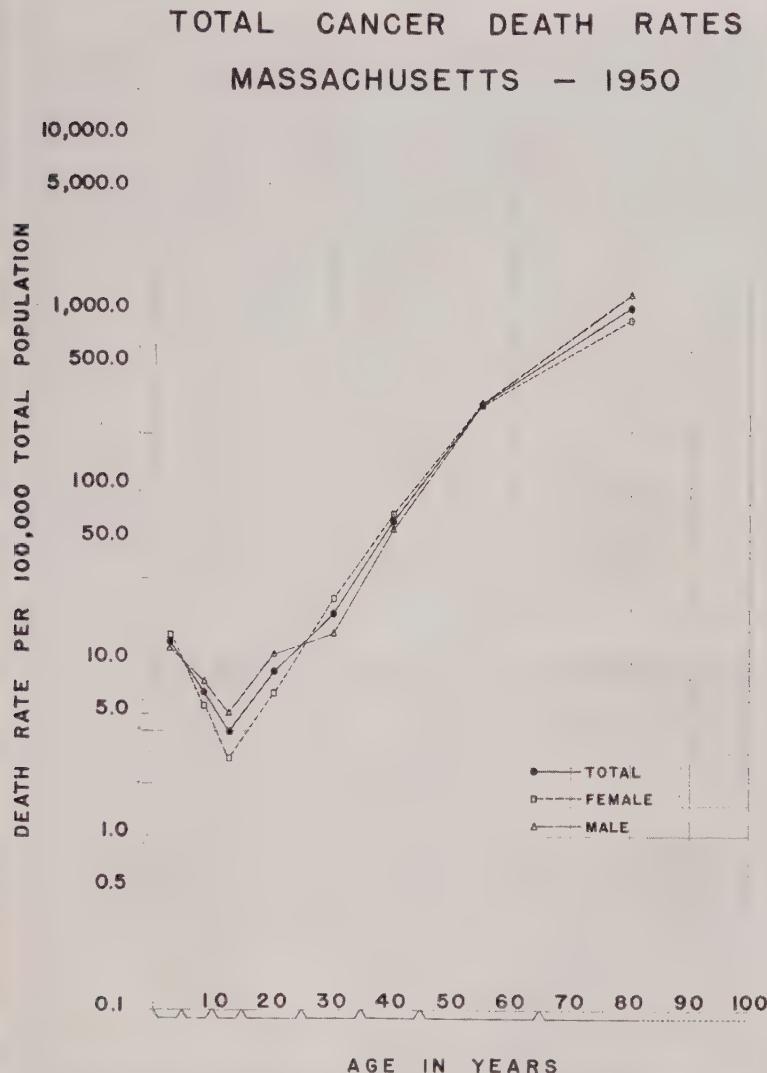


Fig. 314.—A graph on semilogarithmic paper of the cancer death rate per hundred thousand population in Massachusetts for the year 1950. The statistics upon which this chart was based are among the most accurate available. Note the rapid increase of the prevalence of cancer with increase in age, both for males and for females.

Interestingly enough, there are many species variations in susceptibility to induction of malignant tumors, and it is not infrequent to find that a carcinogen which is effective in one species will not be effective in another. Thus all of the various hydrocarbons that have been successfully

given an adequate amount of either wheat bran or yeast they may be protected to a considerable degree.

Steiner has demonstrated that there may be extracted from human livers a material which is carcinogenic when injected into rodents. Not

only tumors but tumorlike processes can be produced by chemical means. The absorption of certain arsenic compounds leads to the development of keratosis which may at times become cancerous. The inhalation of benzol fumes in small amounts over long periods of time may lead to a leukemia-like proliferation of the bone

marrow. In general, however, we must look to other sources than chemical carcinogens for the development of tumors in man.

Physical Carcinogens.—Various types of physical stimuli are carcinogenic. It has long been noted in man that carcinoma of the skin is closely related to exposure to sunlight or cold.

Fig. 315.

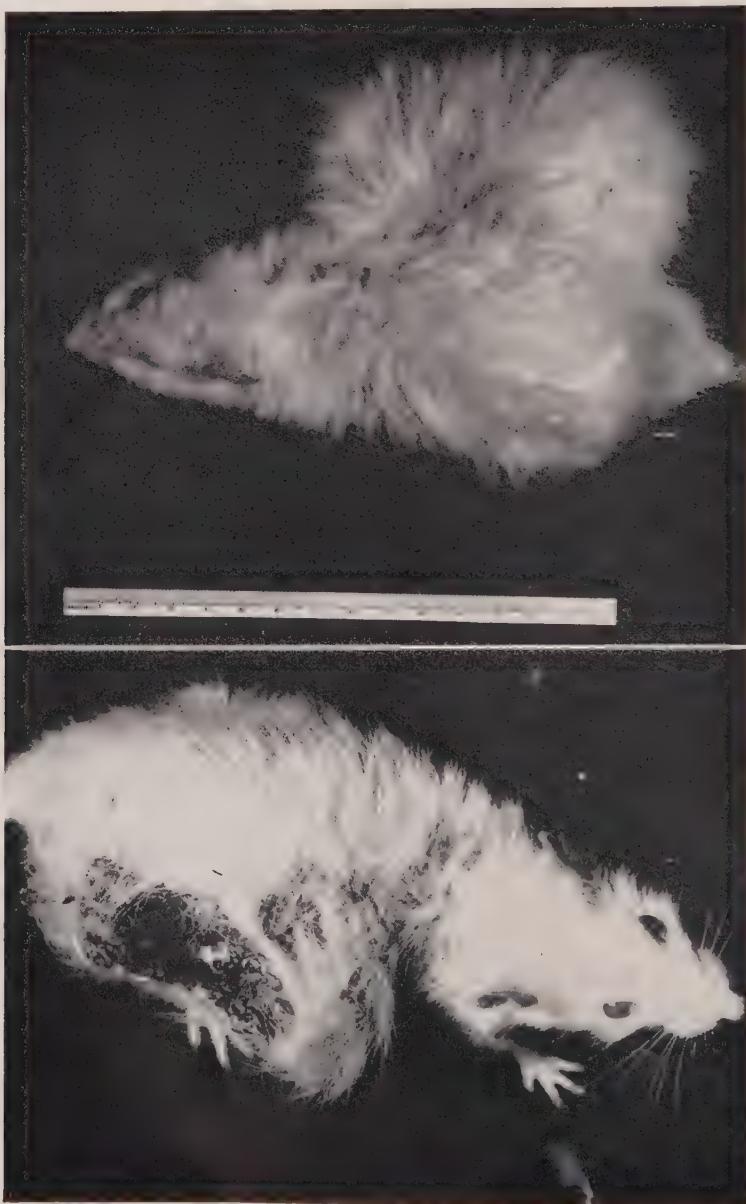


Fig. 316.

Fig. 315.—An adenofibroma of the mammary gland occurring spontaneously in the rat (Slonaker strain). Four and one-half months' duration.

Fig. 316.—Epidermoid carcinoma occurring spontaneously in the rat (Slonaker strain) showing ulceration of the tumor and emaciation of the animal.

Thus carcinoma of the ear is quite common in males. It is rare in women who usually keep their ears covered. There is evidence that much more carcinoma exists among the farmers of the southwest where there is much exposure to ultraviolet light than there is among city dwellers of the north who receive relatively little ultraviolet light. During the war it was noted that carcinoma of the lower lip developed with surprising frequency among some of the younger men exposed to the intense sunlight of the tropics.

be carcinoma of the lung, probably induced by minute amounts of radon in the inspired air.

Trauma as a Carcinogen.—It is doubtful that a single trauma can lead to the production of a cancer. The incidence of carcinoma in scars is somewhat higher than in adjacent normal skin, but here the development of the tumor can be ascribed to the abnormal environment of the cells in the scar rather than to the trauma from which the scar arose. Medico-legal claims for compensation for development of a tumor ascribed to trauma are not infrequent, but



Fig. 317.—An advanced epidermoid carcinoma of the lower lip showing the destruction of the normal mucosa, the swelling and ulceration caused by the growth of the tumor. Man 76 years old. One year's duration.

Ionizing radiation is an important carcinogenic factor. Many of the early workers with roentgen rays received excessive radiation on their hands, which led to the development of radiation dermatitis with later development of carcinoma (Fig. 319). Some of the New Jersey watch-dial workers, who had ingested radioactive material which was selectively retained in bone, developed osteogenic sarcomas. It has been demonstrated that leukemia is more frequent among those chronically exposed to slight overdoses of radiation than among the general population. There is beginning to accumulate evidence that among the Japanese exposed to the atomic bomb radiations at Hiroshima and Nagasaki there is abnormally high incidence of leukemia.

The pulmonary disease from which workers in the uranium mines of Central Europe had long been known to suffer has been shown to

rarely have a basis in fact. The criteria essential before a positive relationship between a tumor and a given trauma can be considered are as follows: (a) the part in which the tumor arose must be proved normal prior to the injury; (b) the tumor must develop in a reasonable length of time following the trauma, a minimum of three weeks and a maximum of three years; (c) the tumor must be of a type that could originate from the cells traumatized; and (d) trauma must be adequate to produce tissue disruption and ecchymosis.

Chronic Irritation as a Carcinogen.—Chronic irritation has long been blamed as a source of tumors, both benign and malignant, although but little experimental evidence exists to support this theory. Nevertheless, there is a considerable body of clinical observation to back it up. It is rare that cancer appears in normal tissue. Its appearance on buccal mucosa in

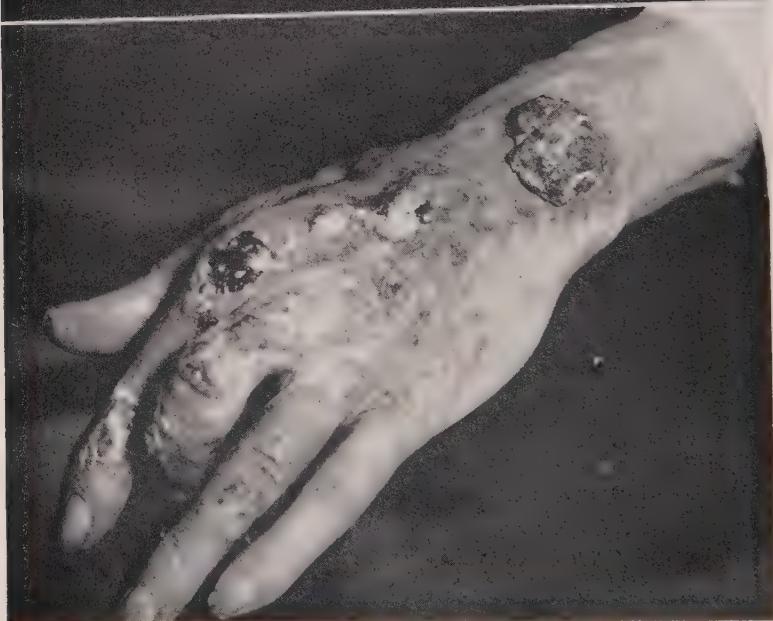
Fig. 318.



Fig. 319.

Fig. 318.—Multiple epidermoid carcinomas and keratoses developed secondarily to repeated exposure to oil and tar over thirty years. Carcinoma had previously been excised from this same area. Man 68 years of age.

Fig. 319.—X-ray dermatitis and multiple carcinomas developing in a physician following fifteen years of repeated small exposures to x-ray radiation. Man 83 years of age. Five years' duration.



relation to a jagged tooth, or on the gum as a result of the irritation of an ill-fitting plate is too frequent to be regarded as due to chance alone. On the other hand, few regions are subject to as much chronic irritation as the palm of the hand and yet the development of a tumor in that location is exceedingly rare. The increase in prevalence of carcinoma of the bronchus has aroused much interest in cigarette smoking as a possible cause. It is believed that the repeated repair following chronic injury ultimately leads to a mutation among the proliferating cells or otherwise provides a stimulus for uncontrolled growth.

Virus-Induced Tumors.—There is no known virus-induced tumor in man. The common wart, verruca, is a local hyperplasia and keratinization of the skin which is induced by a virus, but these warts do not become neoplastic. Virus tumors, however, occur in lower animals.

Borrel's concept of virus-induced neoplasia was established by Ellermann and Bang when they proved that fowl leukosis was a virus disease. In 1911 Rous demonstrated that the sarcoma of the chicken was a virus-induced tumor. Since that time many tumors have been proved to be of viral etiology. Proved virus tumors in fowl are myxosarcoma, angiosarcoma,

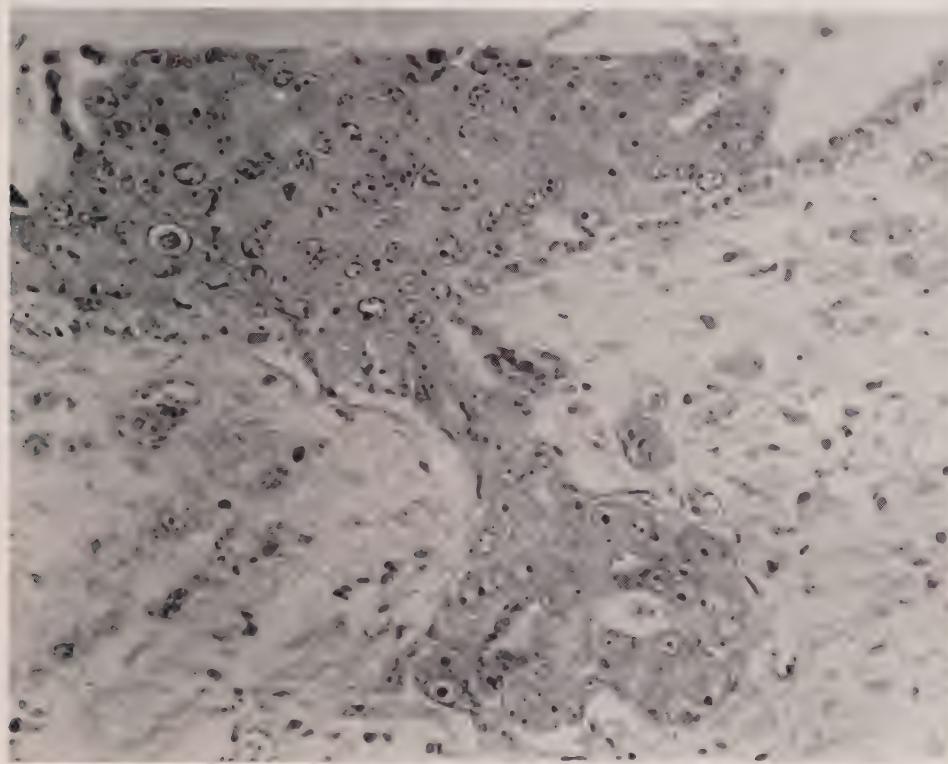


Fig. 320.—A focus of carcinoma arising in chronic cystic mastitis of the breast. Woman, 32 years of age. ($\times 400$.)

Certain changes in cells in or adjacent to foci of chronic irritation may be recognized as characteristic and so often are followed by the development of cancer that they are spoken of as "precancerous" (Fig. 320). In the course of such changes, the cells may become malignant, but not invasive at first. Such a condition is termed "carcinoma in situ."

Hormonal Carcinogens.—Women with estrogen-producing ovarian tumors show excess incidence of endometrial carcinoma. Experimentally, estrogen hormones have produced benign and malignant tumors in rats and mice. Autotransplantation of ovary to spleen in mice leads to production of granulosa-cell carcinoma in the transplanted fragment, probably due to pituitary hormonal stimulation.

fibrosarcoma, and endothelioma; in rabbit are Shope fibroma, papilloma, and carcinoma; in frogs are adenoma and adenocarcinoma of the kidney.

Viruses may be difficult to demonstrate. Electron micrographs of T-phage infected bacteria fail to show the virus, unless many serial sections of the bacteria are examined. Under some circumstances, tumors known to be viral in origin may fail to yield up their virus. For example, when the Shope papilloma becomes a carcinoma, the virus cannot be recovered, though its presence can be demonstrated by serum antibodies.

Cocarcinogens may reinforce a virus: the combined use of tar and Shope virus in the

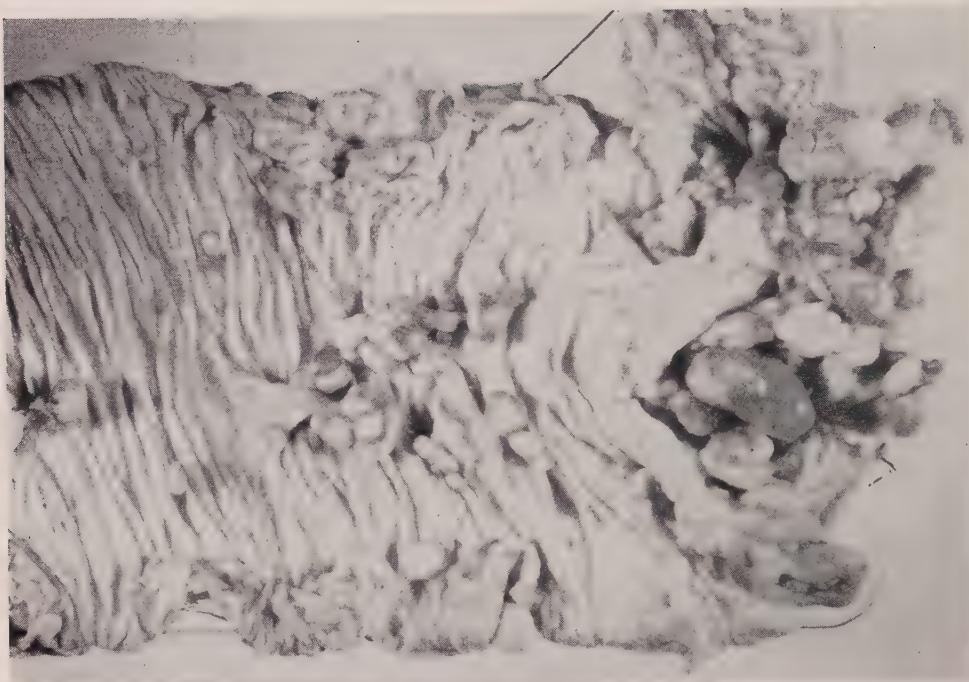


Fig. 321.—Multiple polyposis of the rectum in a girl 13 years of age.

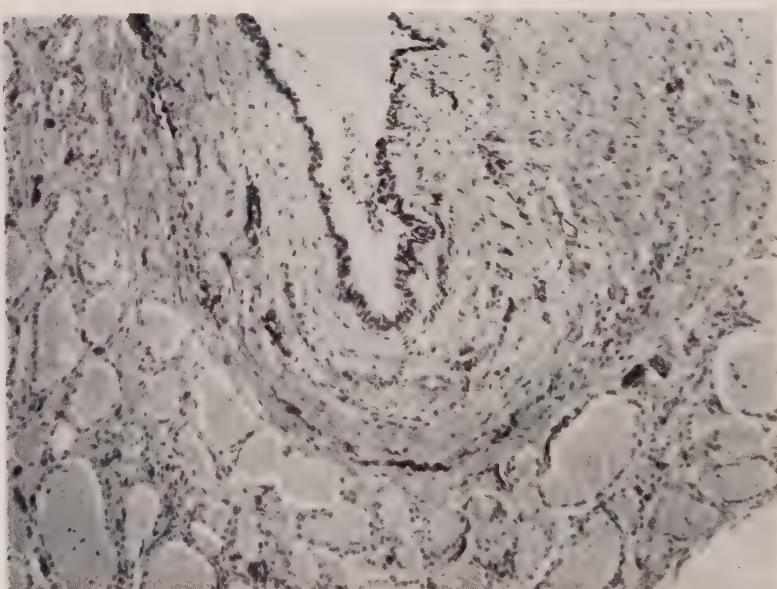


Fig. 322.—Thyroglossal duct cyst, a not uncommon type of embryonic rest. ($\times 120$.) Woman aged 34 years.

rabbit shortens the time necessary for tumor induction, and increases the virulence of the tumor induced.

Heredity.—Practically all information of value with regard to the hereditary transmission of tumors rests upon animal experiments. Far too few human data exist (see page 1347). It has been possible for Little and others to develop by selective breeding strains of mice in which there occurred an abnormally high incidence of cancer and others in which the appearance of cancer was rare. Interestingly enough, an extrachromosomal factor seems to be involved in mammary tumors of mice, as it is possible by suckling mice of a given strain on a foster mother of a different strain to impart to the offspring the characteristics of the foster mother with relation to the tumor rather than the usual characteristics of the offspring's strain. This milk factor is under intensive study and has been shown to be at least in part a protein aggregate with suggestion of relationship to the viruses.

Some cancer families occur in man, but studies of these usually have demonstrated that a predisposing factor to cancer such as multiple polyposis of the large intestine (Fig. 321) is the characteristic which is hereditarily transmitted rather than the tendency to develop tumor itself.

Warren and Gates have demonstrated that there is a tendency to develop multiple cancers (6 times the chance expectation), indicating that an individual susceptibility to develop cancer exists.

Embryonic Rests as a Source of Cancer.—In the course of development of the embryo it is not unusual for groups of cells to fail to differentiate properly and to be segregated in the tissues (Fig. 322). These cells may retain their growth possibilities and develop tumors later on. According to the degree of differentiation of the cells at the time they become separated, varying degrees of differentiation may be seen in the tumors. Most tumors derived from embryonic rests are benign, as, for example, mediastinal cysts. Some by overgrowth of one or more of their components may become malignant. If a tumor of this type consists of only one tissue, it is classified according to the type of tissue which it most closely resembles. Not infrequently, however, tissue components of two germ layers may appear, in which case the tumor is spoken of as a mixed tumor. If there are components of three germ layers present, it is called a teratoma. Mixed tumors and teratomas may vary greatly in their degree of complexity, some being relatively simple, others containing practically all the components of a complete embryo. These embryonic rests tend to occur particularly along the midline and in the gonads. It is possible that those tumors occurring in the gonads represent an abortive parthenogenetic development of a germ cell.

Origin of Malignant Tumors From Benign Tumors.—The question of whether a benign tumor becomes malignant is one that is extremely difficult to answer within any reasonable degree of accuracy. So far as the available evidence goes, benign tumors do not commonly become malignant. Among epithelial

tumors, adenomas of the thyroid, mucosal polyps of the gastrointestinal tract (Fig. 323), and papillomas of the bladder do tend to develop into cancer. Only twice have I seen a carcinoma develop from an adenoma of the breast. Occasionally, however, sarcoma may develop from the stroma of mammary adenomas.



Fig. 323.—Adenocarcinoma arising in mucosal polyp of the rectum. Man, aged 70 years. ($\times 8$)

The extremely prevalent leiomyoma of the uterus may attain a huge size, may undergo a wide variety of types of degeneration, and only with the greatest rarity does a leiomyosarcoma appear. Some of the benign mixed tumors of the parotid may recur and invade locally with clinical evidence of malignancy and may rarely become highly malignant and metastasize widely.

Histologic Classification of Tumors

Tumors are best classified according to the cell type from which they take origin.

In some instances where the type of the cell of origin has not been definitely determined, they are classified according to the tissue from which they arise. The following condensed classification is one that has been found useful in practice:

<i>Benign</i>	<i>Malignant</i>	<i>Tissue of Origin</i>
1. CONNECTIVE TISSUE AND ITS DERIVATIVES:		
Fibroma	Fibrosarcoma	adult fibrous tissue
Myxoma	Myxosarcoma	embryonic fibrous tissue
Chordoma (rarely)	Chordoma	notochordal tissue
Chondroma	Chondrosarcoma	cartilage
Osteoma	Osteogenic sarcoma	bone
Lipoma	Liposarcoma	fat tissue
2. ENDOTHELIAL TISSUE AND ITS DERIVATIVES:		
Lymphangioma	Lymphangioendothelioma	lymph vessels
Hemangioma	Hemangiendothelioma	blood vessels
Glomus tumor Carotid body, aortic body and jugular glomic tumors	Multiple hemorrhagic sarcoma Malignant glomic tumors Myeloma Leukemia (leukemic and aleukemic phases) Endothelial sarcoma (Ewing) Endothelioma Synovioma Lymphosarcoma (including Hodgkin's) Reticulum cell sarcoma Thymoma Mesothelioma Mixed mesenchymal sarcoma	cutaneous glomus internal glomus bone marrow bone marrow bone marrow lining cells of body cavities synovia lymphoid tissue lymphoid tissue thymus mesothelium mesenchyme
Mesothelioma		
3. MUSCLE:		
Leiomyoma	Leiomyosarcoma	smooth muscle tissue
Rhabdomyoma (largely restricted to congenital tumors of heart)	Rhabdomyosarcoma	striated muscle tissue
Myoblastoma	Myoblastoma	striated muscle tissue
4. ELEMENTS OF NERVOUS SYSTEM:		
Neuroma		nerve tissue
Neurofibroma		nerve sheath tissue
Neurilemmoma		nerve sheath tissue
Meningioma		nerve sheath tissue
Ganglioneuroma	Sympatheticblastoma	sympathetic ganglion cells
Nevus	Malignant melanoma	nerve sheath or endings (?)
Carcinoid	Carcinoid	specialized nerve endings
Glioma (well differentiated only)	Neuroblastoma	primitive nerve tissue
Paraganglioma	Neurocytoma	primitive nerve tissue
Pheochromocytoma	Neuroepithelioma	primitive nerve tissue
Glioma (well differentiated only)	Retinoblastoma	glial tissue
Paraganglioma	Glioma	
Pheochromocytoma	Paraganglioma	
Pheochromocytoma	Pheochromocytoma	adrenal medulla or accessory tissue
5. EPITHELIUM:		
Papilloma		pavement epithelium
Polyp		glandular epithelium
Cystoma		glandular epithelium
Adenoma	Malignant adenoma (well differentiated cancer)	glandular epithelium
	Adenocarcinoma (moderately differentiated cancer)	glandular epithelium
	Carcinoma simplex (poorly differentiated cancer)	glandular epithelium
	Epidermoid carcinoma (epithelioma)	pavement epithelium

<i>Benign</i>	<i>Malignant</i>	<i>Tissue of Origin</i>
5. EPITHELIUM—Cont'd		
	Basal-cell carcinoma Transitional-cell carcinoma Embryonal carcinoma Adenoacanthoma Adamantinoma (potentially malignant) Papillary adenocystoma (often malignant) Chorioneplithelioma	basal layer of epidermis transitional epithelium undifferentiated epithelium mucosal epithelium enamel organ glandular epithelium trophoblasts of placental villi
Hydatid mole		
6. MIXED—DERIVED FROM MORE THAN ONE GERM LAYER OR MORE THAN ONE DERIVATIVE OF A SINGLE GERM LAYER:		
Dermoid cyst Mixed tumor of salivary gland (rarely malignant)		ovary salivary gland
Adenomyoma	Adenomyosarcoma Mixed tumor of kidney (practically always malignant)	renal anlage
Hamartoma	Carcinosarcoma	any organ
7. TERATOMA (USUALLY ONLY ONE ELEMENT BECOMES MALIGNANT):		
Teratoma Teratoma	Teratoma Teratoma	gonads embryonic rests

Effect of Tumors on the Total Organism

A tumor may affect the organism in several ways, first, by its mere physical presence, particularly if it presses upon a vital structure such as the brain or a hollow viscous such as the intestine (Fig. 324). As it grows it may erode adjacent tissues or ulcerate with serious hemorrhage or infection. It may have active physiologic functions that have profound effects upon the organism, as is seen in the case of functioning tumors of endocrine glands. Thus, a functioning tumor of the anterior pituitary will produce gigantism in children or acromegaly in adults. A tumor of the parathyroid will produce hypercalcemia at the expense of the bone calcium, resulting in osteoporosis, and deformity. The large excretion of calcium salts in the urine may contribute to production of renal or vesical calculi. A chorioneplithelioma of the testis may produce large amounts of female sex hormones with the development of female secondary sex characteristics by the person in whom it appears.

At times, a malignant tumor will produce a peculiarly severe malnutrition combined with anorexia known as cachexia. This condition is usually associated with ulceration and secondary infection of the cancer and may not be so

much an effect of the cancer itself as an effect of the products of tissue necrosis and bacterial growth.

Histologic Grading of Malignant Tumors

The basis for histologic grading of malignancy was first indicated by von Hansemann, who pointed out that, as a rule, poorly differentiated tumors (Figs. 325 and 326) were more malignant than the better-differentiated tumors. This principle has been used in a rather casual way for a number of years by pathologists in estimating the malignancy of tumors. Broders developed it into a method of arbitrary estimation of the degree of clinical malignancy of a tumor based on the differentiation of its cells. This method was first applied to epidermoid carcinomas where keratinization provides an easily determined index to the degree of differentiation. Thus, tumors that ranged from 100 to 75 per cent differentiation were considered in Grade I (Fig. 327) from 75 to 50 per cent in Grade II, from 50 to 25 per cent in Grade III, and 25 per cent to 0 in Grade IV, the most malignant. This system provided a ready rule-of-thumb and became quite popular.

As time passed, it became apparent that factors other than differentiation were

of importance. Today, when histologic grading is carried out, weight is given primarily to differentiation, but, in addition, mitotic activity, infiltrative growth, and amount of stroma are also considered. It soon became apparent that the prognosis afforded by means of histologic grading was erratic and inaccurate when applied to individual cases because of marked variation in clinical factors such as duration of the tumor, presence or absence of metastasis, and age of the patient. Consequently, its chief value is in the field of group prognosis and in evaluation of therapy as an aid to estimating the comparability of various series of cases of a given type of cancer.

tumors are uniform throughout in histologic appearance, they may vary from portion to portion, and hence a biopsy taken from one region may give a false impression of the degree of malignancy present in another region. The majority of tumors, however, are surprisingly homogeneous in their morphologic characteristics. Some estimation of the likelihood of the development of metastasis may be made also, tumors of higher grade tending to metastasize more readily than those of lower grade. A metastatic tumor usually shows the same histologic grade of malignancy as the primary from which it came. However, in some instances a higher grade, in other instances a lower,



Fig. 324.—Epidermoid carcinoma, Grade III, occluding the bronchus and producing atelectasis of the lung tissue peripheral to the point of obstruction. Man, aged 44 years.

In the hands of many, the system of using four grades has proved cumbersome, and a system utilizing three grades (Fig. 328) has become widely used. There are several difficulties in accurate histologic grading. While, in general,

may be presented by the metastases. In rare instances, adjacent metastases may present entirely different degrees of differentiation.

The estimation of the histologic degree of malignancy must also take into con-

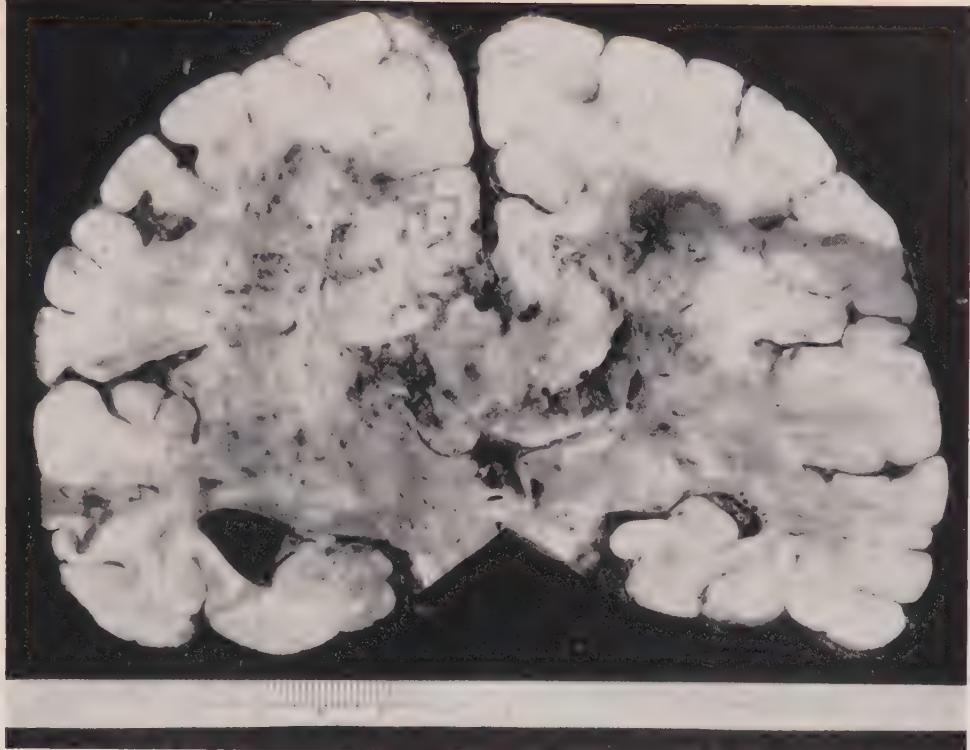


Fig. 325.—A poorly differentiated glioma (glioblastoma multiforme) widely infiltrating brain tissue. Man, aged 50 years.



Fig. 326.—A poorly differentiated adenocarcinoma of the stomach which has infiltrated practically the entire stomach. Woman, aged 48 years.

Fig. 327.

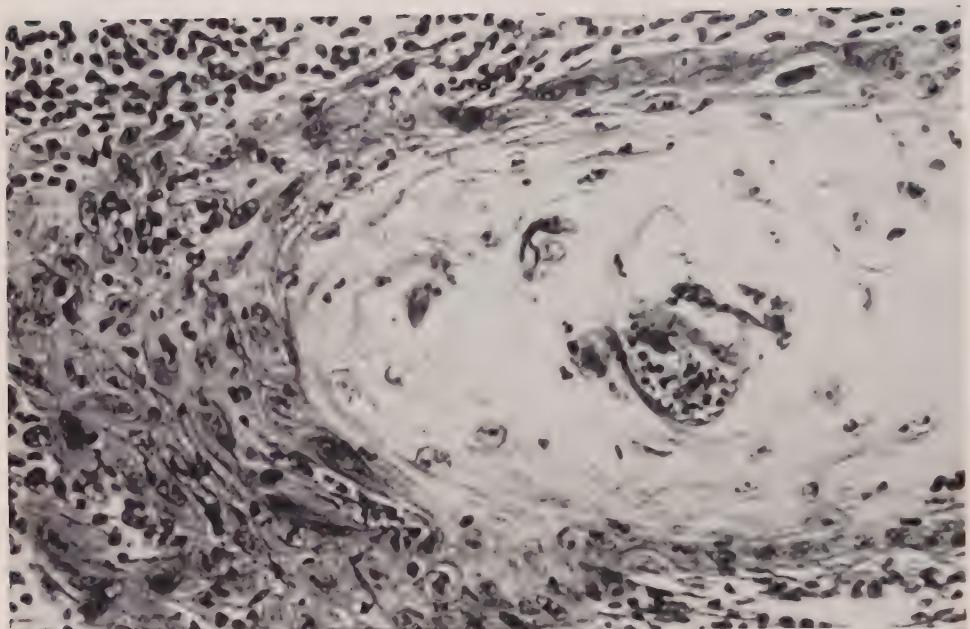


Fig. 328.

Fig. 327.—An epidermoid carcinoma, Grade I, of the tongue, showing the characteristic formation of heavily keratinized epithelial pearls. ($\times 150$.)

Fig. 328.—Epidermoid carcinoma, Grade III, originating in the cervix uteri. Note the presence of abnormal mitoses and tumor giant cells. No differentiation is apparent. ($\times 300$.)

sideration the primary site of the tumor. Thus, the standards for grading that prove satisfactory in epidermoid carcinoma of the lip would be entirely unsatisfactory in carcinoma of the bladder. In certain types of cancers histologic grading is relatively easy and gives a fairly accurate group prognosis, as, for example, in case of carcinoma of the lip, tongue, cervix, endometrium, large intestine, and thyroid. On the other hand, grading of carcinomas of the breast is difficult; in tumors of the stomach gross characteristics are apparently of greater importance than histologic characteristics, perhaps because most of the gastric cancers are well advanced before being recognized.

In the case of sarcomas, there is but little aid from histologic appearance in determination of the degrees of malignancy. In general, fibrosarcomas without tumor giant cells are relatively slowly growing, and those containing tumor giant cells are of relatively high malignancy (Fig. 329).

Tumor Immunity

There is no evidence of immunity to tumors in human beings. Such evidence as there is emphasizes that an individual who has had one malignant tumor is definitely more likely to develop a second tumor than is a normal person. While cytotoxic sera have been produced for a variety of cells, there has not been developed as yet a serum that attacks neoplastic in contrast to normal cells.

In the experimental animal immunity to transplantable tumors occurs spontaneously at times or may be induced. This may be in the nature of refractoriness to a given type of transplantable tumor initially, or the animal may become refractory following partial or complete absorption or removal of an initial tumor transplant. There is some evidence that this condition is a generalized one rather than specific, in that "immunization" to one tumor may protect against other transplantable tumors. Even injection of tissue from adult or embryo members of the same species jeopardizes subsequent successful tumor implants. This refractoriness, in all probability, rests largely on the genetically foreign character of the transplanted cells. Spontaneous tumors are not influenced in any way by the induction of a resistant state to a transplantable tumor in the same animal.

Since there is no definite tumor antigen and since the cells of any spontaneous tumor partake of the immunologic properties of the host, it has been impossible to establish immunity toward a spontaneous tumor.

A good deal of work in the field of the Shwartzmann phenomenon with relation to tumor has been attempted but no conclusive

results have been obtained. There is some evidence that bacterial toxins or fractions of them will lead to hemorrhagic and degenerative reaction in spontaneous or induced tumors. However, this is not yet clearly established. There has been considerable discussion of the reticuloendothelial system in relation to resistance to tumors, but there is little if any evidence that justifies this. Blocking of the reticuloendothelial system does make it possible for heterologous tumor transplants to take. There is some evidence that some immunity may be produced by the lymphoid cells.

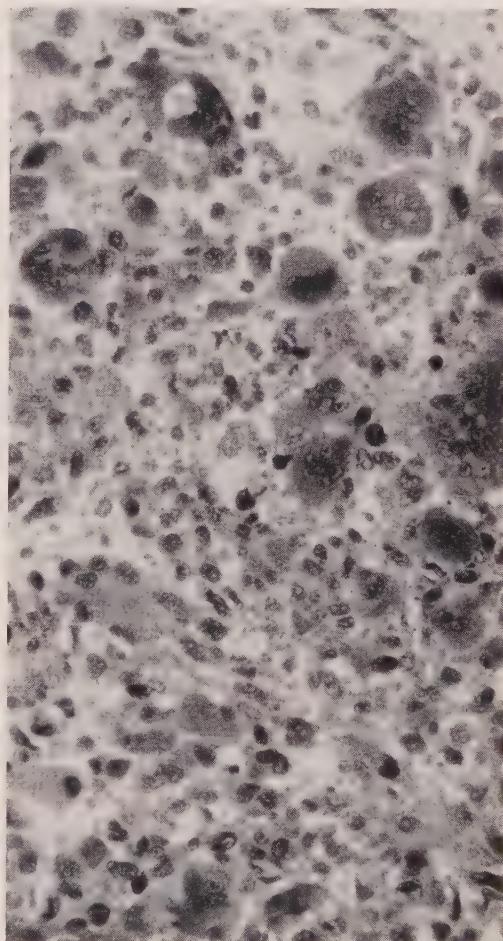


Fig. 329.—Section of an osteogenic sarcoma showing both tumor giant cells (those with the larger and most distorted nuclei) and foreign body giant cells (those with the multiple small nuclei). ($\times 300$.)

Tumor Transplantation

Transplantable tumors have been successfully transmitted from animal to animal for many generations. Mice, rats, and rabbits are the animals commonly used and a wide variety of carcinomas and sarcomas as well as benign

tumors are available. Heterologous transplants may be made from a number of malignant tumors, including those of the human. The anterior chamber of the eye, in rats, guinea pigs, and rabbits (Fig. 330) may be used. The hamster cheek pouch and chorio-allantoic membranes of chick embryos are also serviceable. Such tumors may ultimately adapt themselves to their host, and actually metastases of them have occurred. Tumor grafts will grow fairly readily in embryonic tissue although they will not take in adult tissue. At times, it has been possible to transplant tumors of one species into those of a closely allied species, from the mouse to the rat, for example, if the recipient animal has been previously irradiated. Green believes that stromal incompatibility is one of the important factors for the regression of transplanted tumors.

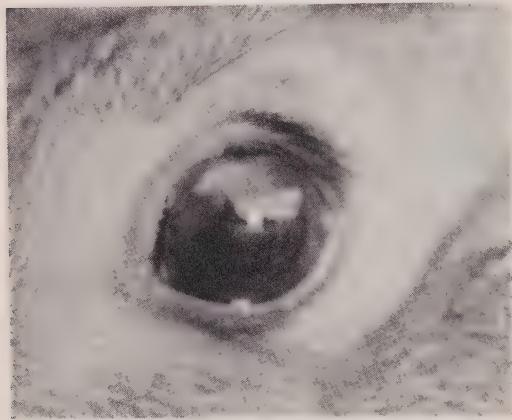


Fig. 330.—Walker carcinoma No. 256 of the rat transplanted and growing in the anterior chamber of the eye of the rabbit.

Serologic Tests for Tumor Diagnosis

There is no satisfactory serologic or chemical test that exists for diagnosis of tumors. Many have been suggested and a few give better results than chance, but none are sufficiently accurate to warrant their practical use.

Metastasis

Since metastases usually closely resemble the parent tumor, at times the problem arises of differentiating a primary tumor from its metastases. Size is of little help, as sometimes primary tumors may be large with small metastases, and at other times the primary may be small with large metastases. I have seen a carcinoma of the breast weighing not over 15 grams produce over 4 kg. of metastases in the liver alone. The histologic character of a nodule is often sufficient to determine whether it is metastatic or not. For example, car-

cinoma of the breast occurring in lymph nodes (Fig. 331) or melanomatous growths occurring in the liver are metastatic. At other times, however, particularly if the cells are poorly differentiated, histology alone will not be a determining factor. As a rule, if there are multiple nodules in an organ or tissue, they are metastatic. A metastasis usually is less invasive than is the primary tumor and tends to be more regular in outline and sometimes even may be encapsulated. There are certain tissues where metastases are common and primary tumors less frequent, for example, the liver or the parenchyma of the lung.

Some tissues are much more frequently the site of metastasis than are others. Because of their large bulk and their abundant blood and lymphatic supply, the lungs and liver are the most frequent sites of visceral metastasis. The spleen is rarely involved in metastasis. This is probably not so much due to any specific abnormality as it is to the fact that there is no lymphatic drainage to the spleen and that the structure of the splenic pulp is not well adapted to the growth of metastases.

Many tumors have curious predilections in sites of metastases, so that sometimes different types of tumor derived from the same organism may have distinctly different characteristics with regard to metastasis. Thus metastases of the papillary adenocarcinoma of the thyroid commonly occur in the regional lymph nodes and in the lungs, whereas metastases of solid thyroid tumors are predominantly found in bone.

In general, metastases show about the same degree of differentiation as does the primary tumor from which they arise. Consequently it is possible quite frequently to estimate shrewdly the nature and growth of a primary tumor from a metastasis. There may be striking variations, however, among the metastases of the same tumor. Thus, in malignant melanoma it is not unusual to find melanotic and amelanotic metastases side by side (Fig. 332). Rarely, metastases are more differentiated (Fig. 333) than the primary tumor. Sometimes they are less differentiated than the primary tumor.

An essential for the establishment of a metastasis is the development of a local

stroma with the connective tissue support and the vascularization necessary to permit growth and metabolic exchange. The methods of metastasis are by the lymph stream, by the blood stream, and by implantation. Carcinomas, in general, tend to metastasize by means of the lymph stream. Such metastases are usually embolic, cells or cell clusters of the tumor invading lymph channels and being carried to other sites, ordinarily the regional lymph nodes. Thus, for example, a carcinoma of the breast commonly metastasizes to the axillary lymph nodes, carcinoma of the serotum to the inguinal lymph nodes, and a carcinoma of the stomach to the lymph nodes along the greater and lesser curvatures.

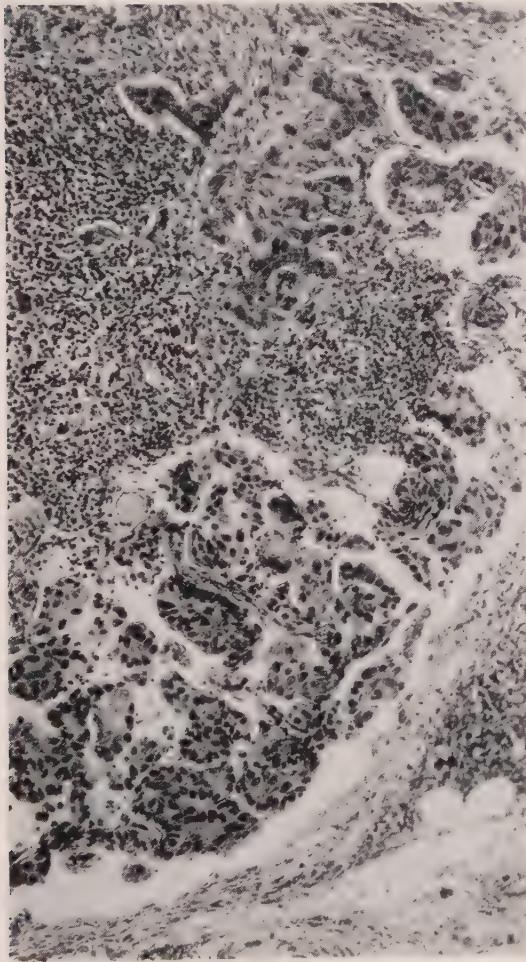


Fig. 331.—Epithelial cells of a carcinoma of the breast invading an axillary lymph node. ($\times 150$.) Woman, aged 55 years.



Fig. 332.—Multiple cutaneous metastases of malignant melanoma to the extremity from a primary focus in the ankle. Note the variation in pigmentation of the metastases as well as their wide disposition. Woman, aged 46 years. (From Daland, E. M.: Radical Treatment of Malignant Melanomas of the Lower Extremities, S. Clin. North America, October, 1947.)

In the initial stages of lymphatic metastasis the tumor cells remain within the lymph sinuses, and, as they multiply there, they invade the lymphoid pulp and pick up supporting stroma. Eventually the entire lymph node will be replaced and considerably enlarged by the metastatic tumor mass. Sooner or later, the capsule will be invaded, but it often remains intact for an appreciable period of time. Sometimes, by vagaries of lymphatic flow, distant metastasis may be the first to appear. For example, a carcinoma of the left side of the lip may

metastasize to one of the posterior cervical lymph nodes on the right side, or a carcinoma of the prostate metastasize to the supraclavicular lymph nodes.

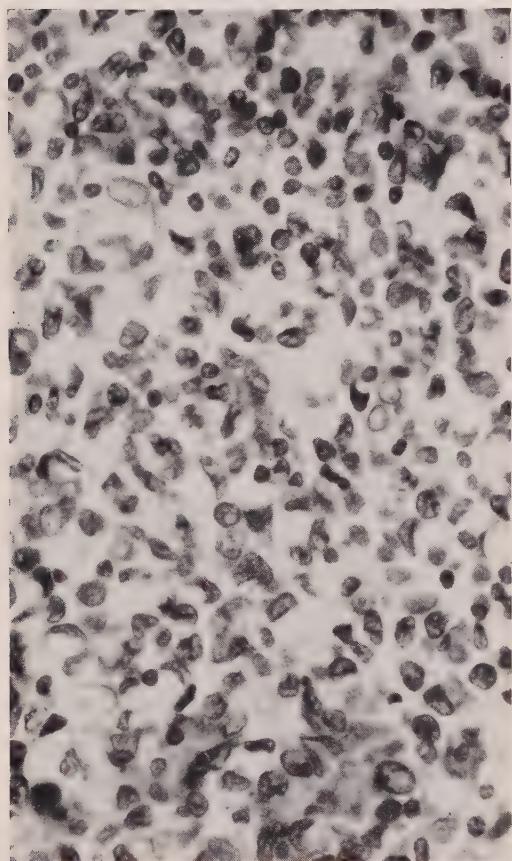


Fig. 333.—Differentiated "signet" cells distended with mucous secretion, metastatic from a poorly differentiated carcinoma of the stomach. ($\times 200$.)

In rare instances, instead of embolic transport, actual growth of tumor cells along the lymphatic channels may occur. This metastasis by permeation again usually leads to the regional lymph nodes. In some instances it is quite possible that continuous growth along a lymph channel does not occur until after embolic metastasis to the node has already taken place.

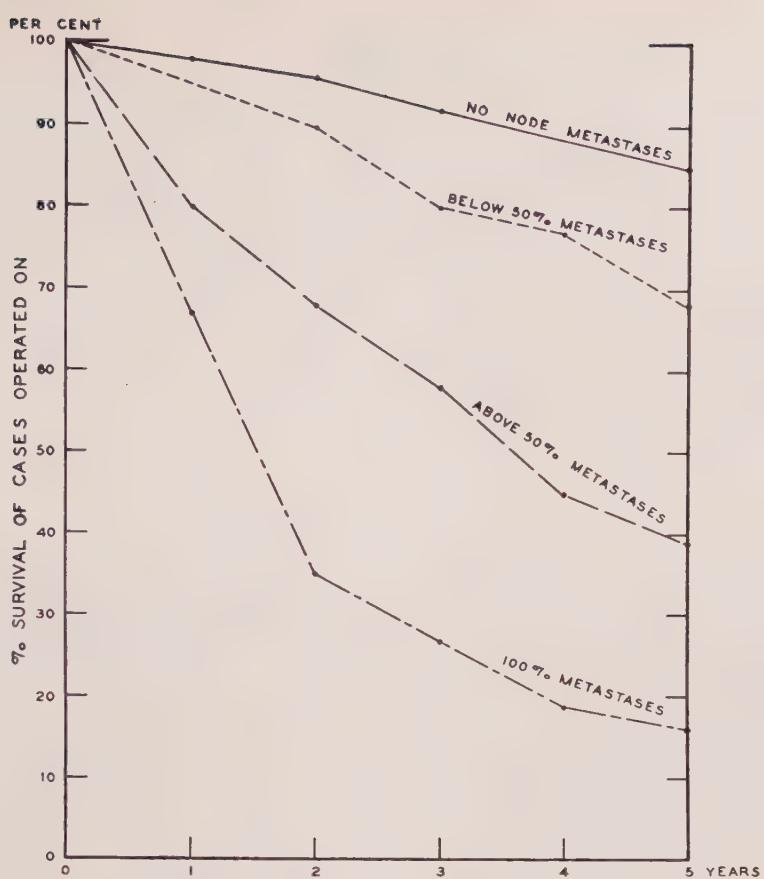
Metastases by means of blood vascular channels are much less frequent than those by lymph channels. This is a more common means of metastasis of sarcomas than carcinomas because of their greater vascularity and the looser texture of the tumor. Certain types of carcinoma of

the thyroid invade near-by veins and establish blood-borne metastasis in the bones. Blood vessel invasion is common in cancers of the large intestine (Fig. 334) and the portal circulation to the liver transports the tumor cells. The most common sites of blood-borne metastasis, however, are the lungs, since all of the systemic drainage passes through the pulmonary capillaries, and hence an excellent opportunity for setting up metastasis is provided. Many cells transported by the blood or the lymph stream to various localities fail to take root in the site to which they are transported.

Metastases may also occur by mechanical transport across serous cavities, as, for example, seeding of the peritoneum with multiple nodules of a primary



Fig. 334.—An adenocarcinoma within the lumen of a thrombosed and organized vein. The heavily stained fibers represent the elastic tissue of the wall. ($\times 250$.)



INFLUENCE OF AXILLARY NODE METASTASES ON SURVIVAL

Fig. 335.—Graph showing influence of axillary node metastasis from carcinomas of the breast on survival.



Fig. 336.—Two masses of basal-cell carcinoma occurring on either side of a scar, also diffusely infiltrated by basal-cell carcinoma. This occurrence was due to incomplete removal of the primary tumor. ($\times 16$.)

ovarian tumor or the growth of tumor cells within serous exudates and transudates.

Metastasis may occur by actual transplantation in the course of a surgical operation, as witness a recent case in which multiple skin grafts were made from the thigh to the inguinal region following excision of metastases of a carcinoma of the vulva. At each donor site a small focus of carcinoma appeared where the malignant cells had been transported on the forceps used to pick up and transplant the grafts.

Secondary metastasis can occur from any metastatic nodule once it has become established. The bulk of a metastasis in the aggregate may be far greater than that of the primary tumor.

Metastasis is facilitated by any method of dislodging cells from the primary tumor, such as traumatization or massage. Coman has demonstrated that carcinoma cells are less cohesive than those of corresponding normal tissues. The role of the spreading factor must also be considered.

The presence or absence of metastasis is probably the most important single factor in the prognosis of a tumor. Therapy of tumors which have metastasized to a distance is rarely successful. Therapy of tumors which have metastasized only locally is greatly influenced by the extent of metastasis to the regional lymph nodes. In cases of carcinoma of the breast, 85 per cent of patients operated upon were living and well at the end of five years, if they showed no metastasis in the axillary lymph nodes. Only 25 per cent were living and well if over half the axillary lymph nodes were involved; and only 15 per cent were living and well after five years with all the regional axillary lymph nodes involved. Thus, the patient without metastasis to the regional lymph nodes had seven times as good a prognosis as the one with all the axillary regional nodes involved (Fig. 335).

Recurrence

Recurrence is a clinical term used to describe the reappearance of a tumor once it has been apparently removed or destroyed. Recurrence indicates that some of the original tumor cells have survived and have eventually multiplied to such an extent that the tumor is again clinically

obvious. Usually recurrence, if it is to occur, appears within the length of time required for a few tumor cells left behind by the attempted extirpation of the tumor to multiply up to a recognizable mass (Fig. 336). There are instances, however, which cannot be explained by the time required for multiplication of cells alone. Thus, I have seen a carcinoma of the breast recur in the scar twenty-eight years after removal of the primary tumor. The factors which kept the cells viable yet dormant over the years and then permitted recurrent growth to occur are difficult to understand. Sometimes, as in the buccal mucosa, new tumors develop in the same general region and may simulate recurrence.

Radiosensitivity

By radiosensitivity is meant the responsiveness of a given tumor to radiation therapy as evidenced by shrinkage with partial or complete regression of the tumor. In general, the so-called law of Bergonie and Tribondeau holds that poorly differentiated tumors respond to radiation well and that the better differentiated tumors respond poorly. There are, however, major exceptions to this. It is extremely important to remember that radiosensitivity and radiocurability are not synonymous. In fact, some of the most radiosensitive tumors are rarely cured. Thus, less than an erythema dose of roentgen radiation will induce marked regression of a lymphosarcoma, but cures of lymphosarcoma by radiation therapy are extremely rarely seen. Moreover, a radiosensitive tumor may acquire radioresistance after treatment without morphologically demonstrable change.

Most of our information with regard to radiosensitivity rests on empirical grounds. For convenience, tumors may be grouped into three general classes from the standpoint of their response to radiation: Radiosensitive tumors will regress with treatment that does no, or merely transient, damage to adjacent normal tissues. Such amounts range from 0 to 2,500 r. when administered in the conventional manner. Radioresponsive tumors are those that will regress when subjected to a course of radiation that does some, but not irreparable, damage to the adjacent normal tissues. The amounts effective in this group range from 2,500 to 5,000 r. Tumors that are no more sensitive than their surrounding tissues are considered radioresistant and require 5,000 r. or above to bring about regression (see also page 172).

The various body tissues vary in sensitivity to radiation, lymphocytes being most sensitive and adult neurons most resistant. In general, the tumors derived from a given cell type tend to follow the relative sensitivity of that type. Vascularity of stroma increases the sensitivity of a tumor, as does rapidity of growth.

Unfortunately tumors that are initially radiosensitive may become resistant if they recur after treatment. This change in response to radiation is not accompanied by recognizable gross or histologic alterations.

Changes Induced in Tumors by Radiation.—While the effects of radiation upon tissues in general have been described in the chapter on radiation injury, certain aspects deserve mention here. The therapeutic effects of radiation on

a tumor depend, first, upon the direct effect upon the tumor cells; second, upon the impairment of the blood supply; and third, upon fibrosis and hyalinization of the stroma which both impairs nutritional exchange and hinders the spread of tumor cells. Much more radiation is required to kill tumor cells in tissue culture than is necessary to kill them in the organism. Tumors, both benign and malignant, vary in their response to radiation according to their cell type, their vascularity, and their stromal support.

Hormonal Effects

In addition to the production of tumors by hormones, mentioned above, certain shifts in hormonal balance exert profound effects on some carcinomas and their metastases. Thus, Huggins demon-

Hypertrophy and Hyperplasia

Hypertrophy is increase in size of an organ or tissue without increase in number of its component units. Hyperplasia is increase in size with increase in number of the component units. Hypertrophy of the heart or of skeletal muscles may result in several-fold increase in size and functional activity without change in number of the muscle fibers. Often the term is loosely used to mean increase in size without regard to the units of structure. For example, "hypertrophy" of the prostate is due chiefly to increase in number of its cells. Because of this loose usage it is best to consider the two processes together.



Fig. 337.—Metaplasia to stratified squamous epithelium occurring in the ducts of the pancreas. ($\times 150$.)

strated that castration caused almost complete regression of some prostatic cancers. Later, estrogens, as stilbestrol, proved to have a similar effect. Some carcinomas of the breast regress for a significant time with administration of androgens or estrogens, the effective agent being determined empirically. Huggins has further shown that bilateral adrenalectomy will cause regression of prostatic cancer.

In no instance have cancers so treated been cured, rather the regression has been temporary, rarely for more than a few years.

In contrast to neoplasia, hyperplasia and hypertrophy are in general initiated and controlled by well-recognized stimuli and cease with their withdrawal. Thus, repeated heavy lifting causes hypertrophy of the muscles involved, but they regress with rest after the lifting ceases. Cortical and trabecular bone thickens with weight-bearing, but atrophies with disuse. In pregnancy and lactation the breast enlarges as a result of hormonal action, the enlargement due to increase in both number and size of the mammary cells, with increased complexity of the mammary units. With disappearance of

the stimulating hormones, regression occurs although the breast tissue does not completely revert to the virginal state.

Hypertrophy may be recognized by an increase in unit size. Hyperplasia may be recognized by an increase in unit number, and if that increase is still taking place when the tissue is studied, mitoses will give visible evidence of the proliferation.

Since both processes call for an increase in cell mass, adequate circulation and adequate food supply, particularly of proteins, is essential. In general, the capacity for hypertrophy and hyperplasia is greatest in the young, and tends to decrease with age.

Certain cells, such as neurons and striated muscle fibers, have no proliferative power in adult life. Others, such as cutaneous epithelium, fibrocytes, or endothelial cells, retain this power indefinitely. Hyperplastic or hypertrophic response is not limitless. The nature of the limiting factors is not known, but blood supply plays an important part.

Metaplasia

Metaplasia is a change in cells of a given tissue to produce a type not normally present. Certain types of metaplasia are frequent, as that from ciliated to keratinized epithelium (Fig. 337), or from fibrous tissue to bone. Other types are rare or unknown. The change is probably not from one adult cell type to another, but rather by influence on primi-

tive cells to differentiate in an abnormal direction. The stimuli may be varied: chronic inflammation or vitamin A deficiency in formation of keratinized epithelium, the presence of calcium salts in formation of bone from connective tissue, motion at the region of fracture in the formation of cartilage from bone. The occurrence of epithelial metaplasia may favor the development of carcinoma (see also page 55).

References

- Biskind, G. R., and Biskind, M. S.: Am. J. Clin. Path. **19**: 501, 1949 (experimental ovarian tumors in rats).
- Broders, A. C.: S. Clin. North America **21**: 937, 1941 (grading).
- Davidsohn, I.: Am. J. Clin. Path. **6**: 172, 1936 (serodiagnosis of cancer).
- Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Co.
- Gates, O., and Warren, S.: A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears, ed. 2, Cambridge, 1948, Harvard University Press.
- Greenstein, J. P.: Biochemistry of Cancer, Academic Press, New York, 1947, 389 pp.
- Hartwell, J. L.: Survey of Compounds Which Have Been Tested for Carcinogenic Activity, U. S. Public Health Service, Bethesda, Md., 1941.
- Hueper, W. C.: Occupational Tumors and Allied Diseases, Springfield, Ill., 1942, Charles C Thomas.
- Huggins, C., and Johnson, M. A.: J. A. M. A. **135**: 1146, 1947 (prostatic cancer, therapy).
- Li, M. H., and Gardner, W. U.: Cancer Research, **9**: 35, 1949 (experimental ovarian tumors in mice).
- Papanicolaou, G. N., and Traut, H. F.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, 1943, The Commonwealth Fund.
- Rous, P.: Harvey Lectures **31**: 74, 1935-1936 (virus tumors).
- Shimkin, M. B.: Cancer **4**: 1, 1951 (duration of life in cancer).
- Steiner, P. E.: Internat. Abst. Surg. **76**: 105, 1943 (carcinogenic agents from human sources).
- Warren, S.: Ann. Surg. **117**: 585, 1943 (criteria for traumatic or occupational causation).
- Wynder, E. L., and Graham, E. A.: J. A. M. A. **143**: 329, 1950 (tobacco and lung cancer).

Chapter 19

THE HEART

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INTRODUCTION

The *cardiovascular system* consists of the heart and pericardium, the blood vessels, and the lymphatics. Although the heart and blood vessels are considered separately as a matter of convenience, it is evident that functionally the system is a unit. Embryologically, the primitive heart begins as a slight thickening in the muscular walls of the dorsal aortae. From this beginning, there evolves within the first few weeks of embryonic life a complicated, four-chambered organ. This enlarged part of the vascular system is essentially a pump, provided with valves and powered by thick muscular walls. In spite of this complicated structure it is fundamentally an enlarged artery. The endocardium is lined with endothelium similar to that lining the arteries. The heart as a modified blood vessel is affected by many of the diseases which afflict the vessels, and vice versa. On the other hand, due to the complicated structure of the heart and the strain of maintaining a constant circulation, the heart is subject to mechanical difficulties, infections of valves and muscle to a greater degree than other parts of the system.

Statistics indicate that heart disease is now the leading cause of death, although much of the apparent increase in the death rate from heart disease is relative, being referable to diminution of mortality from tuberculosis, from other infectious diseases, and in the neonatal period. Some workers, nevertheless, feel that there is an actual increase in the prevalence of organic cardiac disease. This may be true of arteriosclerotic and hypertensive heart disease, of which coronary artery disease is a conspicuous part.

PATHOLOGIC PHYSIOLOGY OF CARDIAC FAILURE*

Cardiac failure is a syndrome produced by inability of the heart to maintain an adequate circulation of the blood. If the heart works against a sustained overload, as may be produced by valvular stenosis, hypertension, or myocardial disease in time, it usually becomes unable to deliver a normal output. In other conditions such as thyrotoxicosis, arteriovenous aneurysm, and aortic insufficiency, an output greater than normal may be required. With the development of myocardial fatigue, cardiac dilatation occurs, according to Starling's¹ Law

of the Heart. Increased energy for production of the necessary output is thus supplied, although upon a less efficient basis. This in some manner causes hypertrophy of the involved myocardium, which is then able to maintain a sufficient output without dilatation but still less efficiently. In time, the myocardium again fails, producing dilatation, leading to more hypertrophy and so on until this mechanism is unable to compensate for the overwork. This chain of events is frequently accelerated by acuteness of the underlying changes occurring in the valves, the myocardium or coronary arteries. If the heart is examined under these conditions, one may see dilatation or hypertrophy or any combination of both, depending upon the stage. In some instances of hypertensive disease, marked left ventricular hypertrophy with minimal or absent dilatation may be seen before congestive failure appears. However, with right ventricular overwork a different situation seems to exist; hypertrophy and dilatation develop concurrently.

When the myocardium can no longer maintain an adequate output, the process of heart failure begins. One of the earliest known changes is the retention of sodium ion and water throughout the body, the exact mechanism being unknown.² It is thought the kidney through decreased renal blood flow and the adrenal cortex by its hormones play important roles. As a result, overhydration of the tissues and blood develops, producing an increased blood volume. The blood volume increases until it distends the venous bed sufficiently to cause an elevation of the venous pressure. Concomitantly with this and helping to raise the venous pressure is the effect of "backward failure."³ This means that one chamber of the heart fails to keep up with the amount of blood being delivered to it by the veins, but does produce a cardiac output sufficient to sustain a normal blood pressure and an almost normal blood flow to most of the tissues. The blood accumulating behind the "failing" chamber increases the amount in the corresponding veins, further distends them, and, therefore, augments the venous pressure in that area. This type of failure is called *congestive heart failure*. The symptoms are caused by the stasis and congestion in the affected organs. These occur first in the regions of highest venous pressure, that is, behind the chamber undergoing backward failure. For example, in the case of left-sided heart failure, dyspnea results from congestion of the lungs, and, with right-sided heart failure, edema results from congestion of the extremities. In left ventricular failure, the pulmonary congestion places an

*I am indebted to Dr. Ralph E. Homann, Jr., for the discussion of "Pathologic Physiology of Cardiac Failure."

overload upon the right side of the heart, which, in the course of time, frequently causes right-sided failure, leading to a combination of symptoms, such as dyspnea, edema, cyanosis, orthopnea, and distended neck veins.

"Forward failure," another type of heart failure, is produced by a sudden diminution in the cardiac output.³ This is most frequently caused by acute myocardial disease, which throws an acute strain on the undamaged fibers, as in myocardial infarction. When the intact muscle, by means of dilatation and tachycardia, cannot fill up the arterial system as fast as it drains, the blood pressure falls, the pulse rises, and the picture of shock ensues. This clinical picture may last a few days and then clear up,

and of varying degrees of severity. Clinical and pathologic observations indicate a hypersensitivity phenomenon affecting basically the dense collagenous tissues and the smaller blood vessels of various organs with the greatest damage usually occurring in the heart. (Modified from Griffith.⁴)

In addition to the changes produced in the heart and larger joints, affected also are the lungs, the brain, the skin and subcutaneous tissues, and the membranes lining the various serous cavities.

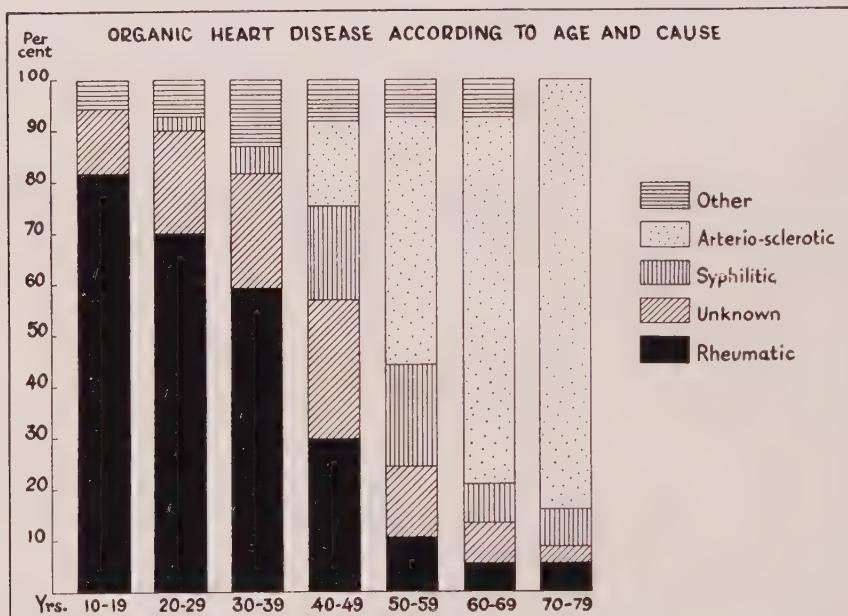


Fig. 338.—Relative frequency of different types of organic heart disease at different ages. The sample consists of 1,001 cases of which 85.4 per cent were clinic patients (cardiac clinic for adults, Bellevue Hospital, New York City) and 14.6 per cent private patients from the practice of the late Dr. John Wyckoff, New York City. (From Wyckoff and Lingg, Am. Heart J., 1926.)

it may cause death, or it more rarely leads to congestive heart failure. Here one almost always finds cardiac dilatation without hypertrophy, as there is not sufficient time for the latter to develop. When hypertrophy is found, it is from an antecedent cause, such as hypertension.

VALVULAR DISEASE (ENDOCARDITIS)

Rheumatic Fever and Rheumatic Heart Disease

Rheumatic fever is a systemic post-streptococcal nonsuppurative inflammatory disease of protean manifestations

The general symptoms of acute rheumatic infection are fever, toxicity, anemia, and leukocytosis, while the more specific clinical manifestations are carditis, polyarthritis, chorea, subcutaneous nodules, erythema nódosum or marginatum, inflammation of serous membranes, pneumonitis, tonsillitis, and epistaxis. Polyarthritis, dramatic and painful when present, is frequently absent or abortive. It reaches its peak among young adults. In a considerable group of rheumatic patients, symptoms at onset are so vague that the disease is not recognized.

The disease is a well-established clinical and pathologic entity which bears some obscure relationship to the infectious types of chronic arthritis called "rheumatism" but should not be confused with acute and chronic arthritis of known bacterial origin.⁵

Rheumatic heart disease refers to the acute, subacute, and chronic changes in the heart which either accompany or result from rheumatic fever.

INCIDENCE AND EPIDEMIOLOGY

Mortality from rheumatic heart disease varies greatly in different geographic areas while variation in the incidence of rheumatic fever is not so marked. At least three climatic factors seem to be important in the incidence of rheumatic fever in any locality. These are low temperature, high humidity, and high altitudes. During World War II, the more

fever mortality rate, 41 per cent, is the same as for Boston. Chavez⁶ reports a high incidence of streptococcal throat infections among the Indian population of Mexico City. In the tropics, where rheumatic fever is of low incidence, cities situated at 8,000 feet or above have a much higher rheumatic fever rate than at sea level. This is probably due to more closely simulating, at these altitudes, the climatic conditions of the temperate zone where streptococcal infections are common.⁷ The lower incidence of rheumatic fever in the tropics is probably dependent upon the decreased number of upper respiratory infections.

Death Rates Show Relative Concentration of RHEUMATIC FEVER in Certain Areas

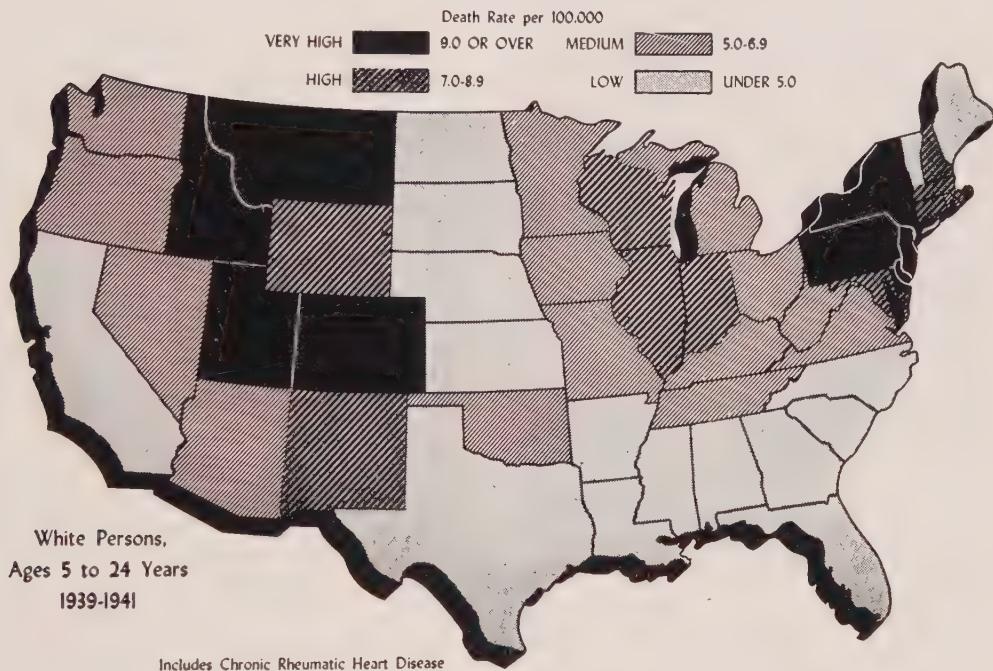


Fig. 339.—Map of the United States showing rheumatic fever mortality statistics in the 5 to 24 age group in white persons, for the years 1939-1941. (Prepared by the Statistical Bureau of the Metropolitan Life Insurance Co.)

severe epidemics of rheumatic fever among Army and Navy inductees were in the North Atlantic seaboard and the Great Lakes areas and the Northern Rocky Mountain states. These localities correspond with the areas of highest mortality from rheumatic fever in peace time as shown by the map, Fig. 339. Cold, wet winter and spring months characterize the Northeastern section and the Rocky Mountain states while the latter region has, in addition, an average altitude of about 5,000 feet.

The high rainfall of the Pacific Northwest is offset by the warmer temperatures produced by the Japanese current. Mexico City, with an altitude of 7,000 feet, has a mild, dry climate, almost the year around and yet the rheumatic

Examination of men under the Selective Service Act (1942) revealed that rheumatic infection accounted for about 5 per cent of rejections for military service.⁸

The disease strikes most frequently in childhood between the ages of 4 and 15 years. It is found frequently from 4 to 50 years, but tapers off rapidly after 50 years of age. During the age period from 10 to 15 years, rheumatic fever and rheumatic heart disease constitute the leading cause of death in the United States. Both sexes are attacked by the disease, females showing a slightly more frequent incidence in a ratio of 4 to 3.

Race.—In a large naval training camp where 212,776 white men were processed, there were

57,141 Negroes. The incidence of rheumatic fever in the white men was 0.138 per cent while in the Negroes it was only about half as high, 0.07 per cent. The Negroes were more reactive to the effects of the disease, however, requiring twice as long for recovery as compared with the white men.⁹

Heredity.—Wilson and associates¹⁰ have shown in a very careful genetic study of rheumatic fever families that in families selected because of the presence of at least one rheumatic child, the distribution of cases follows the general laws of inheritance. Frequency of observed cases was consistent with the hereditary mechanism of a single autosomal recessive gene. Predictions based on such a mechanism were finally realized. The authors concluded, therefore, that susceptibility to rheumatic fever is hereditary. Griffith⁴ believes that so-called hereditary susceptibility may be due to poor nutrition, group crowding, or to a "streptococcal carrier" in the home rather than to a Mendelian recessive character.

Environment.—The incidence of rheumatic infection is eight times greater among children of the slums and poorer classes in New Haven than among children of the well-to-do classes.¹¹ The disease appears to coincide closely with density of population, overcrowding of living (particularly sleeping) quarters, and proximity to low-lying areas near rivers and waterways.¹² All of these factors favor the spread of upper respiratory infections.

Etiology.—Although no definite agent can be designated as the direct cause of rheumatic fever, something is known about the pathogenesis. Theories in the past have considered filtrable viruses, diplostreptococci, and nonhemolytic streptococci. Weintraub¹³ was the first to suggest sensitivity to bacterial products as the probable causal factor. This was accepted by Zinsser¹⁴ who incriminated the nonhemolytic streptococci. Swift and associates^{15, 16} accepted the concept of allergy or hyperergy in rheumatic fever but failed to obtain confirmation of the role of the nonhemolytic streptococci in spite of extensive experimentation.

The second phase of the theory began with the observations of Glover¹⁷ (1930) who described various epidemics of tonsillitis and rheumatic fever in men of the army and air forces in Great Britain. He demonstrated that the peaks of tonsillitis epidemics were followed after two or three weeks by the high points in the rheumatic fever epidemics. Coburn and Pauli¹⁸ in 1932 studied the organisms isolated from the throats of patients who subsequently developed rheumatic fever or a rheumatic re-crucescence. They recovered hemolytic streptococci in the great majority of cases. Subsequent to the throat infections there was usually a quiescent period, followed in two or three weeks by symptoms of rheumatic fever.

The clinical experience of various investigators during recent years has served to substantiate the close relationship between the hemolytic streptococci (Group A) of Lancefield^{19, 20} and attacks of rheumatic fever. This was true among the naval selectees in some of the Naval Hospitals during World War II, where several thousand rheumatic fever patients

were treated. In about two-thirds of the patients there was an antecedent hemolytic streptococcal infection with Griffith²¹ strains. A number of these strains known to be rheumatogenic tended to reappear time and time again in the new patients entering the hospital.²² A very similar condition existed among the Army selectees in various cantonments in this country. The highest incidence of rheumatic fever among the Army personnel during the war was reported from camps in Idaho, Utah, and Colorado. Hemolytic streptococcal infections of the upper respiratory tract at times reached epidemic proportions.²³

The concept of allergy or hypersensitivity to products of Group A streptococci as the causative mechanism in rheumatic fever has not been definitely proved. Indirect evidence is so strong, however, in favor of this idea that it is almost universally accepted. The following characteristics of the disease process suggest an allergic mechanism: (a) the latent period following infection with beta hemolytic streptococci; (b) a clinical reaction similar to serum sickness; and (c) the morphologic analogy between rheumatic lesions and those produced by necrotizing allergic reactions in experimental animals.^{24, 25}

It is pointed out by Murphy and Swift²⁶ that rheumatic fever does not occur spontaneously in animals. Infections due to the Group A streptococcus, which are the forerunners of rheumatic fever in man, do not occur naturally in animals. However, these authors have produced carditis in rabbits by means of multiple skin infections with Group A streptococci that have a striking resemblance to the lesions seen in man. It was not possible to produce these lesions using *Str. viridans* or Group C streptococci as the infecting organisms.

Immunity.—Coburn and Pauli²⁷ studied the immune reactions in the rheumatic fever patient and determined that agglutination, complement fixation, and precipitin tests indicated recent infection with streptococci. Furthermore, Todd²⁸ found a distinct rise in the anti-streptolysin titer of the rheumatic patients' serum as compared with that observed in normal subjects. This has been confirmed repeatedly, but most observers now agree that such high titers indicate recent hemolytic streptococcal infections rather than rheumatic fever, since many nonrheumatic patients have similar concentrations.²⁹

Swift and Hodge³⁰ state that in hemolytic streptococcal infection the nonrheumatic group develops strong titers of type-specific antibodies, the anti-M precipitins, earlier than does the rheumatic group. Coburn³¹ notes that his rheumatic patients were slower in developing high concentrations of both anti-streptolysins and anti-M precipitins than were the nonrheumatic patients with hemolytic streptococcal infections. This seems to indicate that the rheumatic patient is slower in developing type-specific anti-streptococcal immunity than is the nonrheumatic patient. There is further evidence that if satisfactory immunity develops, hypersensitivity decreases, and vice versa. Satisfactory immunity tends to eliminate streptococci promptly, while indifferent immunity allows

the streptococci to localize and survive as a chronic infection. Such a condition may result in continuation of the hypersensitive state.²⁹

THE BASIC PATHOLOGIC PROCESSES IN RHEUMATIC FEVER

One of the important basic lesions of acute rheumatic fever, which occurs in the heart, the joints, and to a lesser degree in other organs, is swelling and degeneration of the collagenous ground substance of the fibrous tissues designated in the earlier stages as *fibrinoid swelling* or *degeneration* and later as *fibrinoid necrosis*. The term *fibrinoid degeneration* was first used by Neumann,³² 1880. Klinge in 1933^{33, 34, 35, 36} brought the term into common usage in his studies on rheumatic fever. The lesions are most pronounced in the collagenous tissue of the heart valves, myocardium, and pericapsular tissues of the larger joints. As the collagen swells, it loses its fibrillar structure, becomes homogeneous and hyaline, and stains intensely with the eosin dye. This reaction is seen conspicuously about the arterioles of the myocardium (Fig. 340). The spaces about the arterioles are broadened by the presence of this substance, which in the acute phase reacts like fibrin to the Weigert fibrin stain. When stained with certain silver preparations, fine black wavy lines may be seen traversing the area. The black fibrils represent the white fibrous tissue fibrils which have lost their ground substance.

THE NATURE OF COLLAGEN

The true nature of collagen is controversial. While it is obviously the fibrillar ground substance which lies between the connective tissue cells, it is not known whether it is secreted by the cells or whether deposited out of the tissue fluid under the influence of the cells. Baitsell³⁷ believes, from his studies on the frog, that collagen can be formed from a fibrin clot in the absence of connective cells. Most investigators agree with Hass and McDonald,³⁸ however, "that fibroblasts perform an indispensable role in collagen formation." Chemically, collagen is composed of several mucopolysaccharides combined with a protein. The nature of the protein is not known. Studies with the electron microscope demonstrate conspicuous cross striations in normal collagen fibers. It has been shown by Wolbach and Howe³⁹ that ascorbic acid is essential for the formation of collagen fibers. Of fundamental importance in the formation of collagenous fibers is not only normal fibroblasts, but also a homogeneous ground substance. The latter is of a mucinous nature and consists of mucopolysaccharides, five

of which have been identified, viz., hyaluronic acid, chondroitin sulfate, A, B, and C, and, last, heparin in small amounts.^{40, 41} As stated previously, little is known about the protein to which these substances are bound.

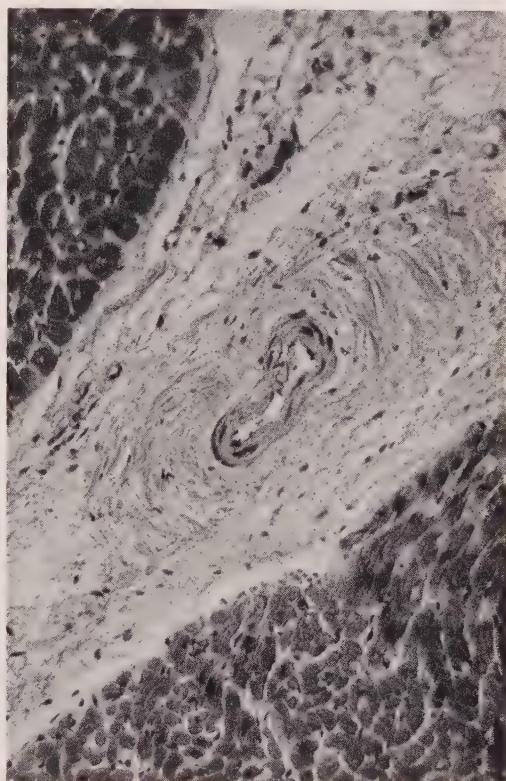


Fig. 340.—Fibrinoid swelling of collagen about a coronary arteriole.

Altshuler and Angevine⁴² state that fibrinoid formation depends on precipitation of acid mucopolysaccharide of the ground substance of the connective tissue. The precipitant may be an alkaline protein derived from the necrosis of tissue or the interaction of the tissue with an injurious agent. Some think that the presence of fibrinoid always indicates an allergic reaction. Since it can be produced by a variety of different reactions, it probably is not specific for injury of any particular type.

It has been shown that cortisone and ACTH exert definite antiphlogistic reactions in allergic inflammations as well as in those due to traumatic or bacterial causes.⁴³ Benditt and co-workers⁴⁴ have shown that the adrenal hormones are capable of inhibiting capillary permeability that is induced by local application of hyaluronidase. It is suggested that the plasticity of the ground substance of connective tissue may be in part under the control of the adrenal steroids.

The exudative and degenerative changes discussed above are soon augmented by

certain proliferative reactions involving the myocardium, cardiac valves, subcutaneous tissues, joint capsules, and at times the pharynx.

The *proliferative lesions* that characterize rheumatic infections of the heart are: (a) a tiny granuloma, microscopic in size, known as the *Aschoff body*, (b) a somewhat similar lesion but of much larger size, the so-called *subcutaneous nodule* found in the subcutaneous tissues about the larger joints, (c) a widespread inflammatory cellular exudate composed of large mononuclear cells, Anitschkow

Aschoff nodule exhibits a central mass of swollen, necrotic collagen. Mononuclear cells infiltrate the loose connective tissue about the central mass like a coronet.⁴⁶ In the early stages of the disease (up to one month) the cells may be small, only slightly larger than lymphocytes. These are believed to be mesenchymal cells. In the next phase (one to three months) many large cells appear with abundant basophilic cytoplasm, each nucleus containing a large nucleolus, the so-called owl-eyed cells. These cells are often multinucleate, containing three to

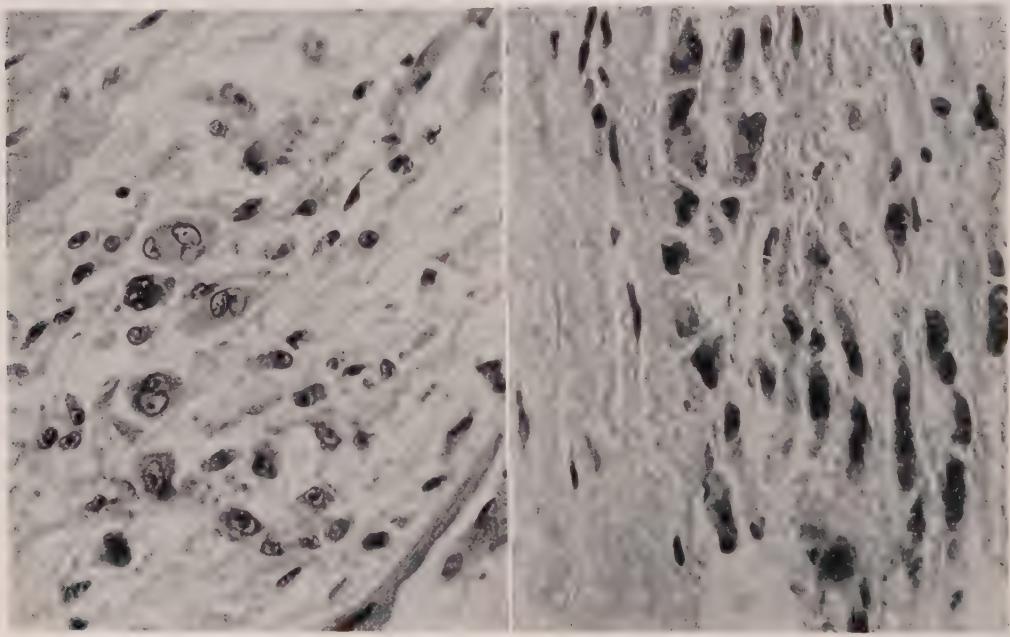


Fig. 341.—Aschoff bodies in the myocardium. with giant cells showing basophilic cytoplasm, showing smudging of nuclei. Note necrosis of the collagen in each case.

White male 15 years of age. A, Coronal type
B, Aschoff body in early polarizing phase

histiocytes, and occasional eosinophiles, and (d) a healing or repair in which fibrous tissue replaces lost functional elements.

The **Aschoff body** was described and interpreted in its true light by Aschoff⁴⁵ in 1904. It is regarded as pathognomonic for rheumatic carditis. The nodules are commonly located in the loose connective tissue near a coronary arteriole. They also occur in the interstitial tissue of the myocardium, in the valves, in the pericardium, and in the adventitia of the aorta. In form they may be globular, elliptical, or fusiform. Commonly the

eight nuclei. The arrangement of the cells in this phase may be coronal, reticular (diffuse), or mosaïc in pattern. In the final phase, lasting roughly from two to four months, the Aschoff nodule is elongated or fusiform, the cells are also elongated and narrowed, the nuclei stain solidly, and frequently fibrillar material appears between the cells, crowding them into rows. The giant cells as well as the mononuclear cells at this stage are transforming into connective tissue cells.⁴⁶ (Fig. 341.)

There have been many suggestions regarding the origin of the Aschoff cells. Klinge³⁵ refers

to them as mesenchymal cells, and perhaps the most widely accepted opinion is that they come from the connective tissues or the mesenchyme. The Aschoff cells are not phagocytic as shown by their reaction to neutral red. This distinguishes them therefore from monocytes, epithelioid cells, and plasmacytocytes.⁴⁷ Murphy^{36a} has demonstrated, apparently, that many of the basophilic, multinucleate syncytial cell masses seen in Aschoff bodies of rheumatic fever patients and experimentally produced Aschoff bodies in rabbits are of myogenic origin. His excellent illustrations are convincing. In the early stages of the nodule a few lymphocytes, plasma cells, eosinophiles, and even polymorphonuclear leukocytes may be present. Anitschkow myocytes are cells with cylindrical nuclei, each nucleus having a barlike mass of chromatin suspended from the nuclear membrane. These cells are found only in the heart and its appendages. In cross section, the nuclei are round with a central mass of chromatin surrounded by a clear field, thus producing the so-called "owl-eye" effect. It is believed that these same cells give rise to the basophilic multinucleate giant cells referred to as the Aschoff cells. Microscopic study of favorable specimens seems to confirm this view (Fig. 341).⁴⁶ As the fibrillary or polarized phase develops the cell nuclei become pyknotic and detailed structure is no longer discernible.

Much of the confusion and controversy relative to the Aschoff body is due to the fact that the lesion is not stable but passes through a cycle of changes. Aschoff⁴⁵ recognized this in his original paper. The chief cells vary markedly in appearance in the different phases, thus accounting for the wide variance in the cell descriptions. The highly characteristic multinucleated giant cells are found usually in only the middle stage.⁴⁶

In the late phase the degenerating ground substance is gradually replaced by connective tissue, and the reticulin, formerly demonstrable by silver stains, loses its argyrophilic property. The Aschoff cells become transformed into fibrocytes. Thus the end result is a fusiform scar, infiltrated perhaps by a few lymphocytes. Aschoff bodies are found in the heart in about 32 to 87 per cent of acute and subacute rheumatic infections.⁴⁹ In healed valvular lesions of the heart they have been reported in from 13 to 50 per cent of cases.^{50, 51}

The subcutaneous nodules of rheumatic fever in children are subcutaneous infiltrations varying in size from 0.5 to 2 cm. They tend to be spherical or oval in shape. They are attached to deeper structures such as tendons or tendon sheaths, periarticular ligaments, fasciae, or periosteum. The nodules are usually somewhat mobile except when attached to the periosteum.⁵² The nodules occur three to four in number on the average, and last four to six days, occasionally longer. On the contrary, the nodules of rheumatoid arthritis may persist for years. Subcutaneous nodules of rheumatic fever are painless and produce no symptoms. Microscopic study reveals a central area of necrosis due to fibrinoid swelling. A middle zone is composed of large mononuclear cells in radial and palisade arrangement. These cells are prob-

ably mesenchymal in origin.⁴⁷ At times, multinucleate forms appear, resembling the Dorothy Reed cells. There is no connective tissue capsule, which renders the periphery of the lesion somewhat indistinct, a condition that is emphasized by the great amount of edema present. The close similarity of the lesion to the Aschoff body is evident.



Fig. 342.—Subcutaneous nodule. Note area of fibrinoid necrosis surrounded by pale edematous tissue supporting many fusiform mesenchymal cells. ($\times 75$) (Courtesy Armed Forces Institute of Pathology.)

Nodules apparently develop in rheumatic fever patients as a result of injury to the subcutaneous tissues since they can be produced by the injection of a variety of substances.⁵³

THE PATHOLOGIC ANATOMY OF RHEUMATIC FEVER

Rheumatic endocarditis or verrucous endocarditis is the most characteristic cardiac lesion of acute rheumatic fever. Tiny, wartlike nodules (verrucae), ranging from 1 to 3 mm. in diameter, form along the closing or contact edges of the leaflets or cusps. These are located on the auricular surfaces of the mitral and tricuspid valves and on the ventricular surfaces of the semilunar valves. Occasionally verrucae appear on the mural endocardium of the left auricle and ventricle. The verrucae in the earlier

stage are slightly translucent, later becoming more opaque and gray to tawny in color. They may be single or they may occur in clusters of two or three. The consistency is firm, hence they are not readily dislodged to produce embolic phenomena (Fig. 343). The mitral valve is most frequently involved, followed closely by the aortic. Involvement of mitral and aortic valves together is next in order. The tricuspid is attacked quite

attachment to the mitral valve. They may also occur on the mural endocardium of the left auricle near its base. As recurrent attacks of rheumatic activity occur, new crops of verrucae appear on the damaged valves. As these new verrucae heal, the leaflets gradually become thicker, shorter, and scarred, often beyond any resemblance to the normal structure. The chordae tendineae become shortened and thickened. Calcifi-



Fig. 343.—Acute rheumatic endocarditis. Verrucae are present along the closing edges of the tricuspid leaflets. (Courtesy Dr. O. B. Pratt.)

frequently but less severely than the mitral and aortic valves. The pulmonic valve is rarely affected. The valve leaflets may be swollen and edematous due to fibrinoid swelling of the dense fibrous valvular tissues. The verrucae represent only the superficial reaction to a process which involves the annulus and septa fibrosa of the heart as well.

On microscopic examination the verrucae consist of small thrombotic deposits of agglutinated platelets crowned by a dense hyaline deposit of fibrin. The latter stains intensely red with eosin (Fig. 344). Remnants of a palisading with fusiform cells, probably fibroblasts, arranged with their long axes at right angles to the surface, may be seen about the bases of the nodules, at least in some instances.⁵⁴ Verrucae soon become organized due to connective tissue cells that grow in from the leaflet. Nodules frequently appear on the chordae tendineae near their



Fig. 344.—Section through a verrucous nodule. The dark cap consists of fibrin which is being organized by connective tissue cells from the valve.

cation adds to the rigidity of the leaflet as well as to its deformity. The final result is the "buttonhole" or "fish-mouth" valve of mitral stenosis or the greatly deformed, calcified structure seen in aortic stenosis (Figs. 345 and 346).

Rheumatic myocarditis in the acute stages of the disease is characterized by edema of the interstitial connective tissue, fibrinoid swelling of the perivascular fibrous tissue, infiltration of the connective tissue with cellular exudate, and, most important of all, by the presence of Aschoff bodies. Edema may cause considerable separation of muscle fibers, the spaces between the fibers being infiltrated with lymphocytes, polymorphonuclear leukocytes, occasional plasma cells, eosinophiles and cardiac histiocytes (Anitschkow myocytes).⁴⁸ The cardiac muscle fibers may likewise show parenchymatous degeneration, fatty degeneration, and some loss of cross striations. Rheumatic myocarditis is most readily recognized in the middle phase of the infection when the Aschoff nodules are most typical because of the presence of giant cells.⁵⁵ In the later stages of the infection the edema has subsided and polymorphonuclear leukocytes have disappeared. Many cardiac histiocytes and some lymphocytes and eosinophiles are present. Perivascular areas of fibrinoid swelling are now undergoing transformation back to connective tissue. The Aschoff bodies are becoming polarized with fibrillary bands crowding the Aschoff cells into longitudinal rows. More or less perivascular scarring and at

times extensive replacement of muscle by fibrous tissue may occur even in young adults.^{36, 51} In recurrent infections with chronic valvular deformities, scarring is common and more extensive. Small, widely distributed scars commonly seen in the myocardium of the left ventricle in aortic stenosis are, no doubt, the result of anoxia (Fig. 356).



Fig. 346.—Aortic stenosis. Note fusion of cusps along commissures. History of rheumatic infection. (From Hall and Ichioka, Am. J. Path. 16: November, 1940.)

RHEUMATIC AORTITIS AND ARTERITIS

The *vascular changes* in rheumatic fever, especially those involving the capillaries and arterioles, are of first importance. Alterations in the vascular elements cannot well be separated from those in the muscle proper. Indeed, almost every arteriole and small artery is surrounded by fibrinoid swelling or the later phases such as a connective tissue proliferation or scarring. Aschoff nodules will be present in many of these perivascular zones.

Rheumatic Aortitis.—The gross lesions of rheumatic aortitis appear as raised reddish areas in the intima of the aorta or as a series of ridges extending across the vessel above the aortic valve.^{56a} On microscopic examination the intimal lesions consist of cellular, vascular connective tissue. Lesions develop in the media about the penetrating vessels, producing dense scars infiltrated with mesenchymal cells, cardiac histiocytes, and lymphocytes. The elastic fibers are destroyed in these areas. The muscle fibers of the media often show hydropic degeneration. The adventitia may present a variety of rheumatic changes including fibrinoid swelling, edema, rheumatic arteritis, and perivascular Aschoff bodies. More or less infiltration of the connective tissue with Anitschkow myocytes and lymphocytes is the rule.

Rheumatic Arteritis.—Focal lesions of the arterioles and arterial capillaries and to a lesser degree of the veins are present in most instances of rheumatic infection. These are not confined to the coronary arteries but may be seen in the lungs, pancreas, kidneys, ovary,



Fig. 345.—Mitral stenosis. The mitral leaflets are thickened, fused, and ulcerated. Note greatly thickened chordae tendineae.

testicle, and skin. Histologically the entire thickness of the wall is involved and often the entire circumference. The endothelium is swollen, basophilic in staining, and may be separated from the wall by infiltration of coagulable material. The media is thickened due to edema and fibrinoid swelling. The muscle nuclei tend to disappear, leaving a finely granular or hyaline necrotic matrix. There may be a patchy effect or, as frequently happens, the entire cir-

cumference of the vessel may be involved. (Fig. 347.) Gram-Weigert staining for fibrin reveals deep blue masses of fibrinoid material infiltrating the wall and usually the perivascular spaces as well.^{34, 56b} The media and perivascular space may be infiltrated with moderate numbers of mononuclear cells, but the tissues remain avascular. Heavy staining with hematoxylin or preferably with polychrome methylene blue or thiouin brings out a patchy bluish

Fig. 347.

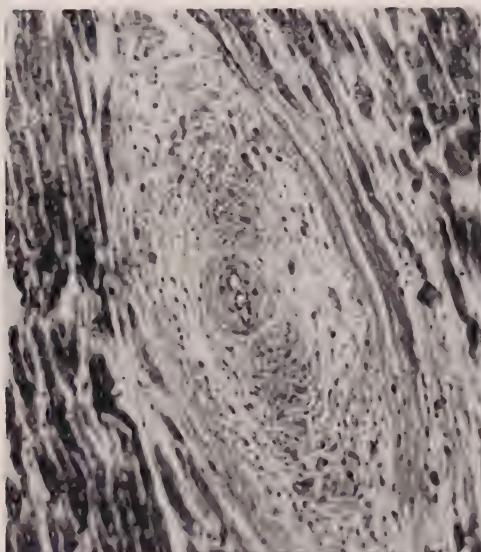


Fig. 348.

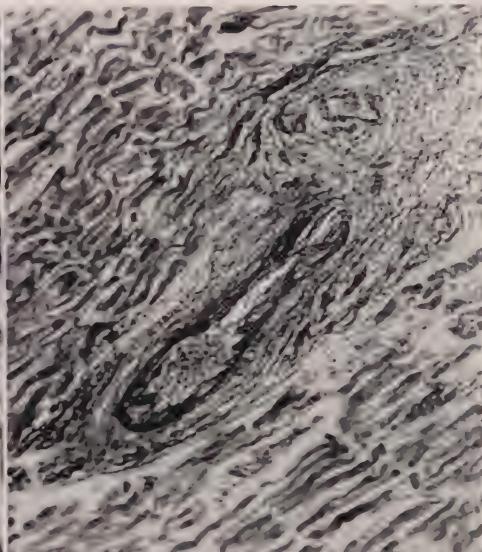


Fig. 349.

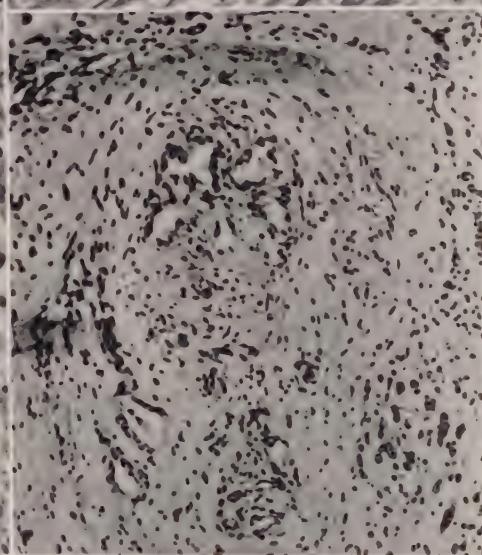


Fig. 350.

Fig. 347.—Rheumatic arteritis. Fibrinoid swelling and necrosis of coronary arteriole and its perivascular collagen. White boy, aged 15 years, who died of rheumatic pancarditis.

Fig. 348.—Rheumatic arteritis showing swelling and proliferation of the elastic tissue.

Fig. 349.—Rheumatic arteritis. Verrucous nodules (fibrin and platelets) almost fill the lumen of this coronary arteriole. Same patient as in Fig. 347.

Fig. 350.—Rheumatic arteritis. Late stage in recanalization of artery. Arterial wall almost obliterated by scar tissue.

coloration of the media in about half the cases of rheumatic infection. The stainable material, called chromatrophic substance, is not demonstrable in the nonrheumatic controls.^{57a} The internal elastic membrane of the arterioles suffers damage in rheumatic infections in the form of swelling and fragmentation. Reduplication of elastic fibrils may be part of the process. (Fig. 348.) Not infrequently, fairly large arterioles in active rheumatic infection exhibit an exudative and necrotizing panarteritis identical with lesions of periarteritis.^{57b} A verrucous endarteritis is observed occasionally in arteries of the myocardium. Small hyaline, eosinophilic nodules project into the lumen of the vessel. These are probably platelet thrombi identical with the verrucae of the cardiac valves. (Fig. 349.) Finally, musculoelastic hyperplasia of the intima may greatly narrow the lumen, often eccentrically. In chronic rheumatic infection the lumen of the artery may be greatly narrowed, the wall thickened and hyalinized and often fused with the hyaline perivascular fibrous tissue. (Fig. 350.)

Rheumatic Arthritis.—The rheumatic changes in the joints are known less well. According to Fahr⁵⁸ both the synovial membrane and the periarticular connective tissues are the sites of edema, fibrinoid degeneration, and necrosis. Proliferative changes occur in the synovial membrane and large mononuclear cells infiltrate the connective tissue. Intense hyperemia results in the accumulation of serous or serosanguineous fluid in the joint cavity. The articular surfaces are apparently spared. Subcutaneous nodules may develop in the periarticular tissues (see also pages 455 and 1251).

Pleural Lesions in Rheumatic Fever.—Pleurisy may develop in association with polyarthritis or carditis. Pleural effusion is usually present and the pleural surfaces appear slightly opaque due to the presence of a fine film of fibrin. The dry type of fibrinous exudate is not common in rheumatic fever.⁵⁹

Rheumatic pneumonitis is regarded as a distinct clinical entity, although the diagnosis usually depends upon the presence of polyarthritis, carditis, and other signs of rheumatic fever. Anatomically, the condition is difficult to separate from the atypical virus pneumonias. There is no one pathognomonic picture.⁶⁰ Griffith⁶¹ reported an incidence of 11.3 per cent pneumonitis among 1,046 Navy men with rheumatic fever. Grossly, the lungs are large, bluish or purplish in color, firm and rubbery in consistency. The microscopic changes in the lungs include edema, capillary hemorrhage, and hyaline membranes in the alveolar duets. The abundant cellular exudate, both septal and alveolar, in which small and large mononuclear cells are predominant, is one of the outstanding features. Fibrinoid changes and angiitis are often present. (See page 668.)

Chorea Minor (Sydenham's Chorea, St. Vitus Dance).—The word "chorea" (Gr. = dancing) is applied to a number of conditions in which disordered and involuntary movements are characteristic. Chorea minor, often associated with or preceded by rheumatic fever, is seen in childhood and early adolescence. The disease in children is to be differentiated from

Huntington's chorea which is a chronic, hereditary disease occurring usually in adults. A positive history of rheumatic infection in patients suffering from chorea minor varies from 16 to 72 per cent.⁶² In 80 fatal cases of chorea, Sturges⁶³ found at autopsy normal cardiac valves in only five instances.

Chorea is likely to follow the lighter attacks of rheumatic fever rather than the more severe ones. Residual carditis is not severe, as a rule, in the patient with chorea.

Lesions in the brain consist of a diffuse meningoencephalitis of mild degree. Gross lesions are usually absent. Microscopic lesions have been found most frequently in the basal nuclei, where hemorrhage, thrombosis, edema, and perivascular exudation of round cells are commonly seen. Cortical lesions are often present but irregularly distributed. (See also discussion on page 1316.)

Prognosis.—A sharp decline in the incidence and severity of rheumatic fever may occur within the next decade or two. This may well result from prophylaxis and early treatment of upper respiratory infections together with other beta hemolytic streptococcal infections, especially in children and adolescents, by means of antibacterial agents. Another promising approach is through the use of cortisone and ACTH therapy in patients in whom rheumatic fever has already developed.

Barnes⁶⁴ and others have demonstrated that patients suffering from rheumatic fever when treated with the adrenal hormones become afebrile within a few days, polyarthritis clears, while signs of carditis gradually lessen and may disappear. Often, however, symptoms and signs recur after therapy is stopped. Some authors have reported cures especially when treatment is started early.⁶⁵

Syphilitic Heart Disease

In syphilitic heart disease the main cardiovascular lesion is that of aortitis. Lesions of the heart itself are usually due to syphilitic valvulitis or aneurysm of the ascending aorta with dilatation of the ring, resulting in aortic regurgitation, which in turn produces marked hypertrophy and dilatation of the left ventricle. Narrowing or closure of the coronary ostia in syphilis is also dependent on the aortitis. Angina pectoris and other signs of coronary insufficiency may ensue. Fibrous or gummatous myocarditis occurs rarely. The great majority of all syphilitics show gross or microscopic evidence of aortic disease. There is some evidence of valvulitis in about half of these. The aortic lesions are described on page 521.

Syphilitic Aortic Valvulitis or Syphilitic Endocarditis.—The term "endocarditis" is not frequently used for the aortic lesion of syphilis since the process is essentially an extension of the granulom-

atus aortitis downward into the valvular structures. The commissures of the valves tend to be separated by a proliferative process consisting of diseased aortic tissue (Fig. 351). At the same time the disease extends into the free portion of

The valve cusps undergo thickening, eversion, or rolling of edges in about 30 per cent, and retraction in a lesser number of cases⁶⁶ (Fig. 352). The coronary ostia, which may be partially or completely closed by a similar process, now



Fig. 351.—Syphilitic aortitis with vegetative endaortitis. Note smooth, slightly raised plaques immediately above the valve commissures.

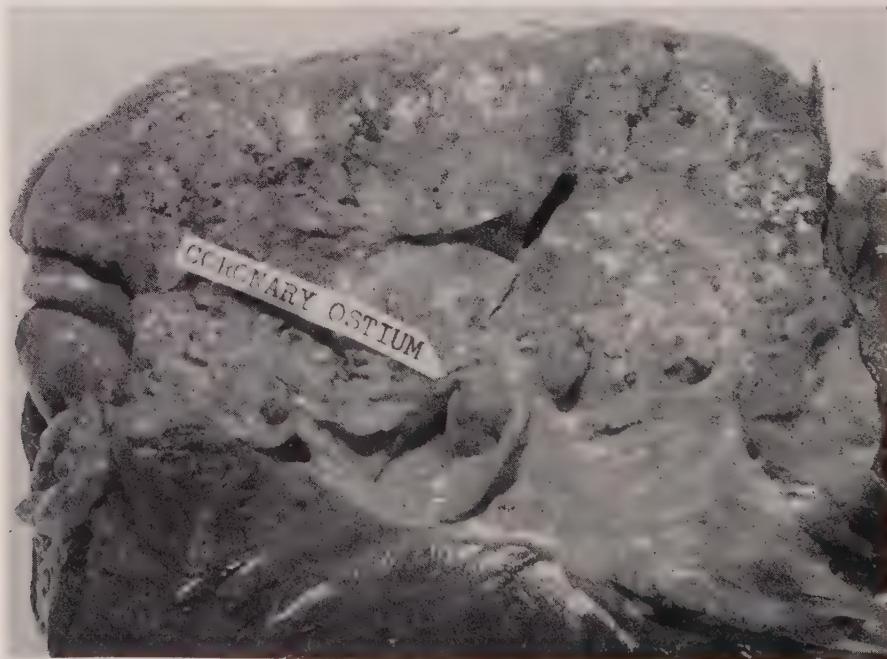


Fig. 352.—Syphilitic valvulitis (late stage). Note spreading of commissures, thickening and shortening of cusps. The aorta is scarred and atheromatous.

the cusps, resulting in adhesions between the lateral portion of the leaflets and the aortic wall of the sinus of Valsalva. The elastic tissue undergoes partial destruction and is replaced by fibrous tissue.

appear well above the upper edges of the valves. Normally, they are located slightly below this level. Apparently the whole valvular attachment becomes sagged due to the loss of elastic tissue.

The valve is now decidedly incompetent. As this process advances, the left ventricle undergoes extreme hypertrophy and dilatation. (See also Fig. 183, page 275.)

Valvular Deformities

Although the majority of valvular deformities are caused by rheumatic infection, some are due to other causes. The effects produced on the cardiovascular system are the same regardless of the cause. It is convenient, therefore, to group them together here. The predominant number of these patients die of cardiac failure. In one series studied,⁶⁷ 114 out of 130 patients died of this cause. By far the greater number of valvular deformities are the result of chronic endocarditis. A minority, however, may be due to degenerative changes such as arteriosclerosis, to congenital cardiac anomalies, to terminal bacterial endocarditis, and to other noninflammatory conditions. It may be difficult clinically to differentiate between valvular disease and insufficiency due to dilatation of the ring. This is often impossible in advanced cardiac failure.⁶⁵

ditis. Congenital lesions of the mitral valve are unimportant. Calcific annulus fibrosus may cause shortening and some basal thickening of the mitral leaflets. The cause of this lesion is not definitely known; at times it is associated with rheumatic heart disease, at other times with arteriosclerosis.

The gross appearance of the valve varies greatly according to the degree of involvement. In severe lesions the leaflets become fused along their commissures, greatly thickened and sclerotic, especially toward the closing edges, while the surfaces are nodular or uneven. There is usually foreshortening of the leaflets causing retraction. The chordae tendineae are remarkably thickened, shortened, and their attachments broadened. (Fig. 345.) Calcification of the valves to a greater or lesser degree is almost constantly present. Ulceration of the thickest part of the deformed leaflet is of frequent occurrence. The result is a stiff, nonpliable tissue with "button-hole" or "fish-mouth" opening in which the valve no longer functions as such but forms a partial barrier to the inflow of

TABLE V
OLD VALVULAR DEFORMITIES (130 CASES) (CLAWSON, BELL, AND HARTZELL⁶⁷)

VALVE	NUMBER	PER CENT	VALVE	NUMBER	PER CENT
Mitral	95	73.0	Mitral alone	44	34.0
Aortic	82	63.0	Aortic alone	32	24.6
Tricuspid	13	10.0	Tricuspid alone	0	0
Pulmonic	3	2.3	Pulmonic alone	3	2.3

Incidence.—The mitral valve is most often affected by chronic deforming processes showing damage in well over one-half of all cases. The aortic is a fairly close second, while the tricuspid runs a poor third and the pulmonic is far in the rear. The incidence of involvement of the various values is presented in Table V.⁶⁷

Mitral Stenosis.—Mitral stenosis is caused by rheumatic endocarditis in almost all instances. Occasional cases are the result of healed subacute bacterial endocarditis. Perhaps this number will increase in the future due to the use of penicillin and other bacteriostatics. A few such lesions are produced by healed gonococcal endocarditis, and rarely by other types of acute bacterial endocar-

blood from the left auricle and fails to stop backflow during systole (Fig. 353).

The microscopic structure consists mainly of dense hyaline fibrous tissue, partly calcified, with cellular, vascularized areas here and there infiltrated with Anitschkow myocytes, a few lymphocytes, and occasional eosinophiles. Hyalinized nodules may project from the surface, or more cellular, partly healed verrucae of rheumatic origin may be present.

These valvular changes, as a consequence of obstruction to the outflow of blood from the left auricle, produce dilatation and hypertrophy of this chamber. In a fairly severe stenosis the auricle attains the size of a man's fist. The endocardium is grayish white, thickened, and opaque. A roughened, tawny

area on the posterior wall, about 1 to 1.5 cm. above the valve ring, is known as MacCallum's⁶⁸ patch. Obstruction at the mitral valve causes back pressure in the pulmonary veins and thence into the pulmonary capillaries, producing in time chronic passive congestion of the lungs. Stasis in the pulmonary capillaries places an extra burden on the right ventricle causing dilatation, hypertrophy, and eventually right heart failure, at least in many instances. The right auricle dilates as the tricuspid ring enlarges, and generalized passive congestion of liver, spleen, kidneys, and other viscera follows.

especially following fibrillation (Fig. 353). Occasionally this is in the form of a ball thrombus. Thrombosis is followed by embolism in a considerable number of cases.

Mitral Insufficiency.—Mitral insufficiency is usually associated with mitral stenosis to some degree, since stiff, retracted, and fused leaflets are unable to close completely. If regurgitation is the main alteration, the left ventricle becomes hypertrophied and dilated. The primary changes then consist of hypertrophy and dilatation of the left ventricle and left atrium, with, secondarily, hypertrophy of the right ventricle, and dilatation finally



Fig. 353.—Stenosis of mitral, tricuspid, and aortic valves due to chronic rheumatic endocarditis. The mitral orifice is a mere slit. Note large thrombus in dilated left auricle.

As these events develop there is increasing cyanosis, dyspnea, tender swollen liver, and ankle edema. Although a low systolic and a small pulse pressure are found as a rule, hypertension is not unknown in mitral stenosis.⁶⁷ The heart has now assumed a characteristic form which is diagnostic in the roentgenogram. The right auricle forms a rounded shadow on the right side, the dilated pulmonary conus and left auricle broaden the shadow to the left.

A number of complications occur in mitral stenosis. Auricular fibrillation is exceedingly common as failure sets in. Thrombosis of the auricular appendage of the left atrium is a frequent sequence,

of both chambers of the right heart. At times the heart becomes greatly enlarged in severe, chronic mitral regurgitation. Marked degrees of mitral stenosis are more common than severe grades of regurgitation and are better supported by the heart.⁶⁷

Mitral regurgitation may be caused by rheumatic infection of the mitral valve, myocarditis, healed myocardial infarction, hypertension with cardiac failure, myocardial failure due to anemia, adherent pericarditis and by compensatory changes in aortic regurgitation.

Aortic Stenosis.—Aortic stenosis is usually the calcified nodular type of valvular deformity. The degree of

stenosis varies greatly but it is frequently severe. The lesion is much commoner than was formerly supposed. Out of a study of 490 healed valvular deformities, 200, or 41 per cent, were calcified nodular aortic valves.⁶⁹ While there is a wide range in age, the greatest number fall in the sixth and seventh decades. When the aortic valve alone is involved, males predominate over females by 3 to 1. In combined mitral and aortic lesions males predominate by 2 to 1.

age, the increased weight being due chiefly to hypertrophy of the left ventricle. The obstruction to the blood stream due to a narrowed, calcified aortic orifice greatly increases the work of the left ventricle.

Microscopic examination of sections through the calcified valves show much dense hyaline fibrous tissue which is interrupted here and there by large calcific deposits. The cusp is usually bulbous near the closing edge, and masses of cal-

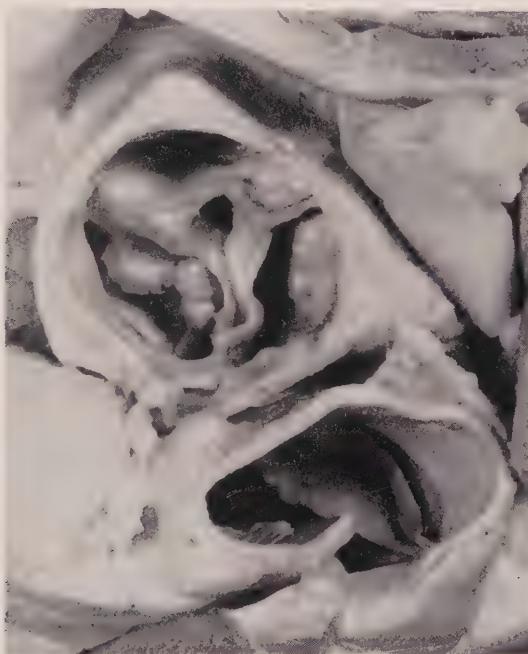


Fig. 354.—Nodular calcific aortic stenosis. Note the perpendicular slitlike opening. White man, 60 years of age, with a history of rheumatic infection at 12 years. Heart weight, 715 grams. (From Hall and Ichioka, Am. J. Path. 16: November, 1940.)

The gross appearance in advanced aortic stenosis is characteristic. Due to fibrous thickening and calcification, the closing edges of the cusps stand out rigidly. The commissures are fused for 0.5 to 1.5 cm. and may be one-half to one centimeter in thickness and well calcified. On the ventricular side, buttresses of calcific material usually reinforce the cusps at their bases. Calcified nodules are often found in the sinuses of Valsalva. The orifice of the valve is reduced by the above changes to a small irregular hole with rigid edges or to a mere slitlike opening. (Fig. 354.) The heart weighs between 500 and 600 grams on the aver-

cified material are present. Near the insertion of the cusps and in the proximal one-third or more, groups of engorged capillary blood vessels are seen. Large mononuclear cells and lymphocytes infiltrate the area in about half of the hearts studied. Occasionally, Aschoff bodies are seen. (Fig. 355.)

Recent clinical and pathologic studies of aortic stenosis indicate that the great majority of cases are the result of rheumatic infection.⁶⁹⁻⁷² Mönckeberg⁷³ (1904) classified many of the solitary aortic lesions as arteriosclerotic in origin. The condition came to be well recognized under the title "Mönckeberg's aortic

sclerosis." More recent investigators have not supported this theory but, on the other hand, have demonstrated the presence of many stigmas of rheumatic heart disease. Other rare causes are healed bacterial endocarditis, congenital bicuspid aortic valve and subaortic stenosis.

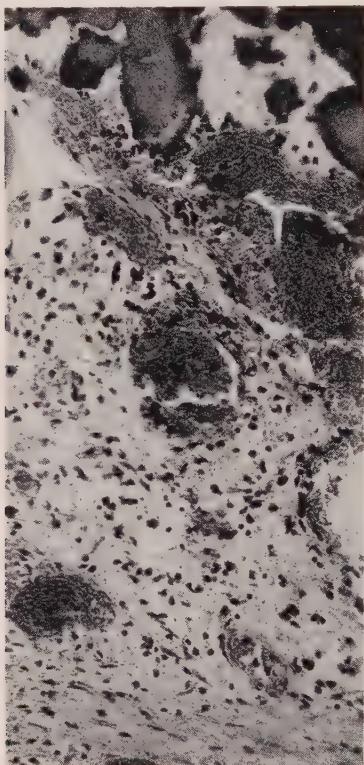


Fig. 355.—Section through the root of a nodular calcific aortic valve. The dark masses at the top are calcified areas. Many dilated capillaries and many large mesenchymal cells are seen throughout. (From Hall and Ichioka, Am. J. Path. 16: November, 1940.)

The primary effect of aortic stenosis is hypertrophy of the left ventricle. Dilatation occurs when the heart begins to fail, which is usually in the late fifties or sixties. The other chambers and valves are likewise not affected until late, if at all. The aorta is small as a rule, and the intima is smooth because of low intra-aortic pressure and reduced blood volume. The coronary blood supply tends to be reduced for the same reasons. Multiple small scars in the myocardium are believed to result from anoxia produced by inadequate coronary flow (Fig. 356).

Clinical symptoms are those of dizziness or syncope due to cerebral ischemia. Sudden death may occur on slight exertion due, apparently, to ventricular fibrillation, but many more die of left ventricular failure. A progressive loud, harsh systolic murmur is generally present in the severe grades of stenosis. Angina pectoris is common.

Aortic Insufficiency.—Aortic insufficiency is common in so-called syphilitic heart disease and in rheumatic endocarditis involving the aortic valve. In syphilitic valvulitis the aortic cusps become separated at their attachments by granulation tissue and undergo thickening and retraction due to fibrosis while the closing edges are thickened and often rolled. At the same time the aortic ring stretches, thus producing a well-marked insufficiency. (See Syphilitic Valvulitis, page 459.)

In rheumatic lesions of the aortic valve producing regurgitation, the anatomical picture is quite similar to that described except that the commissures fail to separate. Rheumatic aortic endocarditis in teen-age children may be strikingly similar to syphilitic valvulitis, especially if the mitral valve is not affected.



Fig. 356.—Scarring in myocardium due to anoxia. The patient was a 20-year-old girl who died of left ventricular failure due to aortic stenosis. Heart weight, 550 grams. (From Hall and Ichioka, Am. J. Path. 16: November, 1940.)

The general configuration of the heart in aortic insufficiency, regardless of the cause, is one of great hypertrophy and extreme dilatation, resulting in a large bulbous left ventricle. Endocardial pockets may be seen in the lining of the left ventricle, with their openings toward the aortic orifice.

The clinical symptoms and signs are characteristic. The pulse is of the Corrigan type with high pulse pressure and low diastolic pressure. The vessels of the neck pulsate and in severe cases the head nods with each heartbeat. A diastolic murmur is usually heard over the sternum or along its left border.

Prognosis is definitely poor in well-developed regurgitation of either rheumatic or syphilitic origin. Death is usually due to congestive failure or intercurrent infection or both.

Tricuspid Valvular Disease.—Tricuspid valvular disease is not important compared with the mitral and aortic lesions. Stenosis is nearly always due to rheumatic infection or congenital heart disease. Rheumatic lesions are overshadowed by similar lesions of the mitral and aortic valves since tricuspid deformities rarely occur alone. When they do occur alone they are usually of congenital origin. Tricuspid stenosis of rheumatic origin is not severe as a rule. Although the orifice is narrowed, regurgitation is likely to be more prominent than stenosis.⁷⁴

Pulmonary Valvular Disease.—Although the pulmonary valve is much less frequently diseased than the tricuspid, it is more important than the latter because of the more serious outlook when it is affected. The pulmonary valve is generally involved alone, rheumatic valvulitis excepted. **Pulmonary stenosis or atresia** is, as a rule, a congenital lesion. In stenosis there may or may not be a septal defect, while in atresia there is always a septal defect. (See page 497.) While rheumatic endocarditis may involve the pulmonic valve, it infrequently produces a deformity.⁷⁵ Bacterial endocarditis of the pulmonic valve with recovery is so rare that it need not be considered.

The *lesion* in pulmonary stenosis is produced by fusion of the valves forming a diaphragm with a small opening in the center. Occasionally, small openings are found at the outer edges of the diaphragm. If the degree of stenosis is severe, hypertrophy of the right ventricle may be extreme. In such instances the right ventricle may weigh more than the left. Vegetative endocarditis is a frequent complication.

Pulmonary insufficiency may result from defective or absent pulmonic cusps and, rarely, rheumatic or syphilitic valvulitis.⁷⁵ More frequently it is part of a general dilatation of the right heart with right-sided failure, including both tricuspid and pulmonic valves (relative insufficiency).

Bacterial Endocarditis

Bacterial or infective endocarditis is characterized by the presence of septic

thrombi (vegetations) on the endocardium, chiefly the valve leaflets and cusps. Although these deposits may be small, they are usually massive and therefore interfere to some degree with the proper functioning of the valves. There is fever, toxemia, cardiac murmurs, often with signs of congestive failure and cardiac enlargement. The presence of petechiae in the skin or conjunctivae are suggestive of bacterial endocarditis but are not pathognomonic. Of the two kinds of bacterial endocarditis, the *subacute* is by far the more common and is less fulminating, lasting from six months to two years. The *acute* is less frequently seen, but it is rapidly fatal within a few weeks. The designation *malignant endocarditis* was used in the past to signify the acute and fatal course of this disease. *Ulcerative endocarditis* is likewise an older term, discarded because it is not accurately descriptive, only occasional cases being truly ulcerative.

Predisposing Conditions.—Infection of a normal cardiac valve by an organism of low infectivity such as *Streptococcus viridans* occurs only rarely. In other words, this organism in the great majority of cases becomes implanted on damaged cardiac tissue. In the younger age groups, rheumatic infection is the chief despoiler of the heart. Thus it is that a previous rheumatic endocarditis exists in the majority of cases of bacterial endocarditis. Von Glahn and Pappenheimer⁷⁶ believe that the latter condition is engrafted on leaflets in which an active rheumatic process is present. They point out that rheumatic recrudescences may occur at any age.

Cardiovascular congenital defects also prepare the soil for invading organisms. Abbott⁷⁷ reported subacute bacterial endocarditis in 17.6 per cent of 555 instances of congenital cardiac disease of clinical significance.

Pathogenesis.—Two possibilities have been cited as the mechanism of infection: (1) That the initial lesion is the result of bacterial emboli. This depends on the assumption that the valvular leaflets are vascularized. (2) That the leaflets are infected directly from the blood stream. While some authors⁷⁸ maintain that the normal valves contain blood vessels, Gross⁷⁹ believed that vascularization is present only after inflammation of the valves has occurred. Valves may be well vascularized in their proximal parts but sparsely if at all toward their free borders. The most widely accepted idea as to pathogenesis seems to be that of direct implantation of bacteria from the blood stream. The thickened, fibrotic valve is exposed to trauma by the force of the blood stream, causing erosion of endothelial surfaces and thus exposing areas where platelets, fibrin, and bacteria may be deposited. Bacteria present in the blood stream have a tendency to pre-

cipitate out, due to the action of immune bodies. Weiss⁸⁰ has reported ten cases of subacute bacterial endocarditis in which tonsillectomy or extraction of teeth immediately antedated the onset of symptoms. Kelson and White⁸¹ estimate that 1 case in 4 follows some dental procedure.

SUBACUTE BACTERIAL ENDOCARDITIS

Subacute bacterial endocarditis or *endocarditis lenta* is caused by *Streptococcus viridans* in the great majority of cases and by the gonococcus or influenza bacillus in occasional instances. The latter two organisms may also produce the acute type, while *Str. viridans* seldom does.

The masses are distinctly friable, and thus particles are from time to time carried away by the force of the blood stream to lodge in some distant organ (Figs. 357 and 358). In some instances destructive changes occur, such as perforation or aneurysm of valve flaps. Blumer⁸³ noted perforation eight times and aneurysm seven times among 150 autopsies. Vegetations tend to localize on the auricular surfaces of the mitral or tricuspid valves, probably beginning along the closing edges as in acute rheumatic endocarditis. Part of a bulky vegetation may involve the undersurface

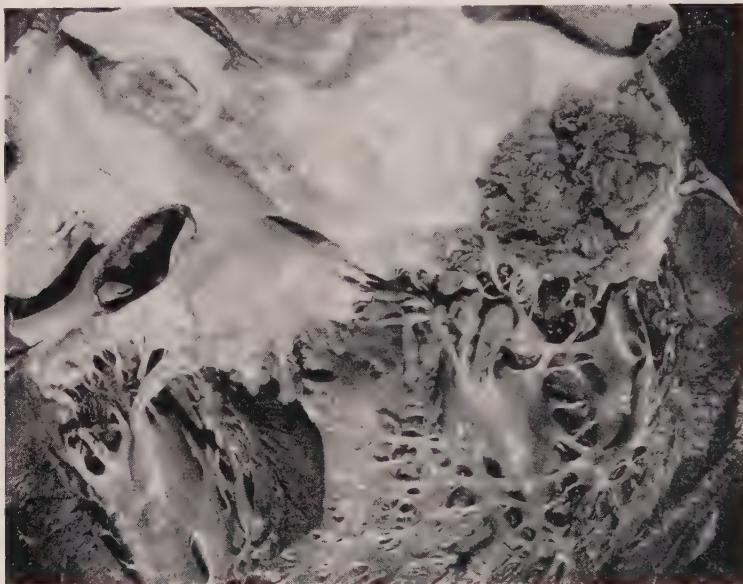


Fig. 357.—Subacute bacterial endocarditis of mitral valve. Note the large vegetation on the wall of the left auricle and the involvement of the chordae tendineae.

Age and Sex.—Subacute bacterial endocarditis may occur at any period from childhood to old age. The greatest incidence, however, falls between the ages of 15 and 30.⁸² Males are more frequently afflicted than females by a ratio of nearly 2 to 1.

Endocardial Lesions.—The valves and adjacent areas are the sites of a proliferative process in which small granular or larger polypoid masses become implanted. These vegetations vary in color through gray, tawny, reddish or dark brown. The tawny or light brown color is due to the presence of fibrin, the reds and browns result from fresh or altered red blood cells which may be caught in the clot.

of the valve near its free edge. The ventricular surfaces of the semilunar valves are attacked primarily although the sinuses of Valsalva may at times be more or less filled with septic thrombi.

In addition to localizing on the valves, in the subacute form of the disease vegetations may spread upward from the mitral valve over the proximal part of the mural endocardium of the left auricle or downward over the ventricular endocardium. The latter is seen usually in connection with the aortic valve. The chordae tendineae may be involved from lesions on the mitral or tricuspid valves. Occasionally, diseased chordae are rup-

tured by the strain on the valves from the systolic blood pressure (Fig. 357).

Microscopic examination of a valve leaflet with its bulky vegetation reveals in most instances a thickened fibrous leaflet infiltrated with large and small mononuclear cells and Anitschkow myocytes. The bulbous vegetative part, according to Moore,⁸⁴ consists of a central core of necrotic tissue, capped by a mass of red-staining fibrin in which purplish-staining colonies of bacteria are embedded. Polymorphonuclear leukocytes are usually confined to small collections within the fibrin. Granulation tissue or, at least, proliferating fibroblasts extend from the valve leaflet into the fibrinous mass. As a rule, bacterial masses are present in the periphery of the fibrin clot as well as in its substance in a position to seed the blood stream constantly with organisms (Fig. 359). Occasionally, the bacteria are deeply embedded in fibrin, and in such cases there may be no septic embolic lesions.

The virtual absence from the vegetations of polymorphonuclear leukocytes is of first importance. It is probably due to the limited vascularization of the cardiac valves and, hence, failure to develop an intense local vascular inflammation. This is one of the factors responsible for continuation of the infection. Friedman and associates⁸⁵ in their experimental work with dogs found the reaction to *Str. viridans* infection different on the heart valves as compared with other foci in the body. All other foci called out leukocytes and healed by scar formation. Valvular lesions increased in size by deposition of

fibrin. In vitro experiments by these authors demonstrated the growth of *Str. viridans* (a) in a serum suspension of red blood cells, (b) a luxuriant growth of organisms in fibrin, (c) no growth of *Str. viridans* in a serum suspension of white blood cells. These experiments emphasize

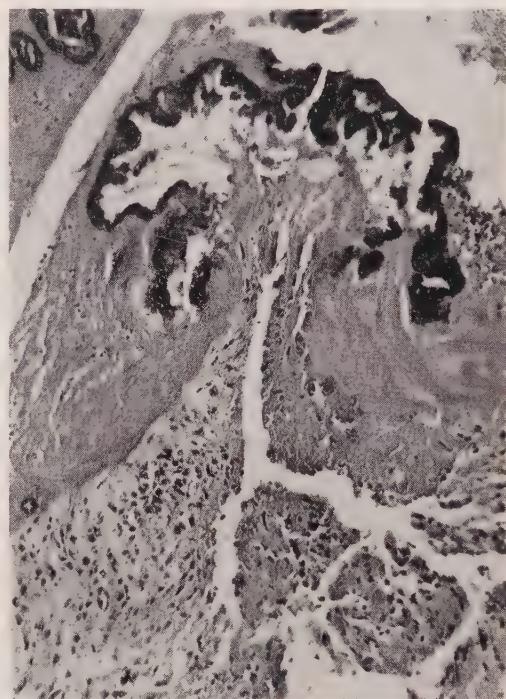


Fig. 359.—Section through a vegetation of the mitral valve in subacute bacterial endocarditis (same heart as in Fig. 357). Note the dark masses of bacteria at the top, partly embedded in fibrin. The thickened valve leaflet (below) is diffusely infiltrated with large mononuclear cells indicative of chronic rheumatic endocarditis. Note necrotic core (right center) which appears to involve part of the valve leaflet. A few polymorphonuclear cells are seen in the fibrin.

the protective value of an adequate leukocytic response and indicate that fibrin forms an excellent medium for bacterial growth. Furthermore, fibrin protects the bacteria from contact with chemical and other therapeutic agents designed to destroy them.

Embolic Lesions.—The most dreaded complication of subacute bacterial endocarditis is the tendency to cast off septic thrombotic material into the blood stream. Since in the majority of instances vegetations are located on the mitral or aortic valves, emboli most frequently enter the systemic circulation. In 72 cases of subacute bacterial endocarditis and 17 cases of acute bacterial endocarditis, Claw-



Fig. 358.—Subacute bacterial endocarditis of the mitral valve with bulbous type of vegetation.

TABLE VI
RELATIVE EMBOLIC INVOLVEMENT OF ORGANS IN BACTERIAL ENDOCARDITIS

	SUBACUTE BACTERIAL (72 CASES)		ACUTE BACTERIAL (17 CASES)	
	(NO.)	(PER CENT)	(NO.)	(PER CENT)
Petechiae	21	29.0	3	18.0
Infarct, spleen	34	47.0	7	41.0
Infarct, kidney	30	42.0	7	41.0
Paralysis	12	17.0	2	11.8
Cases with embolic processes	48	67.0	10	59.0
Embolic glomerulonephritis	35	55.0	2	12.0

son⁸⁶ found embolic involvement of the various organs as shown in Table VI.

In a small proportion of persons afflicted with bacterial endocarditis the vegetations are localized on the tricuspid or pulmonic valves. Emboli in such instances enter the pulmonic circulation, producing septic infarcts and lung abscesses. The pneumococcus and staphylococcus localize on the pulmonic valve relatively frequently. The tricuspid valve is affected most often by hemolytic streptococci and *Staphylococcus aureus*, and not by gonococci as is currently believed. Mycotic aneurysms of the pulmonary arteries occasionally result from a right-sided bacterial endocarditis. The clinical picture is that of pneumonitis, pleuritis, and their sequelae.

Active Cases of Subacute Bacterial Endocarditis Without Bacteriemia.—

IMMUNE REACTIONS.—Every internist has observed patients with active subacute bacterial endocarditis in whom the blood culture was consistently negative. Keefer⁸⁷ estimates that 15 to 25 per cent of all cases of infective endocarditis belong in this group. It should be borne in mind that patients with bacterial endocarditis possess immune bodies in their blood capable of destroying the infecting organism, *Str. viridans*. Friedman and associates⁸⁸ estimate from experiments on animals that human blood may be able to destroy approximately one billion *Str. viridans* organisms per hour. If relatively few organisms enter the blood stream from the heart valves, the blood is rapidly sterilized and repeated cultures may be negative. Abundant antibodies in the blood stream tend to cause bacteria to precipitate out and thus may cause them to localize on the cardiac valves. That bacteriemia in bacterial endocarditis is due to an overflow of organisms from the vegetations into the blood stream seems to be proved by instances in which the blood stream becomes sterile after removal of a focus such as vegetations on an arteriovenous fistula or from a patent ductus arteriosus.^{88, 89} In other words, the organisms ordinarily enter the blood faster than the immune bodies can destroy them.

ACUTE BACTERIAL ENDOCARDITIS

The acute type of bacterial endocarditis is a fulminating, acute infection of the cardiac valves which terminates fatally within from two or three weeks to two months. Fortunately, it is a rare disease

constituting less than 1 per cent of all types of heart disease and of endocarditis.⁸⁴

Age and Sex.—The disease may occur at any age but is commonest between 50 and 55 years. Males are infected more often than females by almost 3 to 1. Undamaged hearts are attacked in some instances, but the disease is more common following rheumatic infection or congenital heart disease.

The organisms most frequently responsible for the acute lesions are hemolytic streptococci (about 50 per cent), pneumococci, *Staph. aureus*, *H. influenzae*, occasionally gonococci, and a variety of other organisms.

Other bacteria reported rarely are *Staph. albus*, *Str. viridans*, colon-typhoid group, the Pasteurella and Brucella groups. Infection of the cardiac valves in the acute form of the disease is usually secondary to some disease caused by the organism present on the cardiac valves. For example, in pneumococcus pneumonia a small percentage of patients may develop pneumococcus endocarditis; likewise, occasional cases of hemolytic streptococcal endocarditis are secondary to puerperal fever. Staphylococcal endocarditis may follow pimples, boils, or carbuncles of the skin. Osteomyelitis was formerly the commonest source of staphylococcal endocarditis but the advent of chemotherapy has, no doubt, reduced the number of such secondary infections.

Acute Endocardial Lesions.—These are very similar to those described under the subacute form of the disease. Perhaps the greatest difference is the tendency in the acute disease to produce larger, globose, relatively smooth vegetations (Fig. 360). This tendency is well illustrated in the infections caused by *Staphylococcus aureus*, pneumococcus, gonococcus, and the influenza bacillus. Ulcerative lesions of the valves are encountered more frequently than in the subacute disease, occurring most often in hemolytic streptococcal infections. The aortic valve is commonly the site of such lesions which exhibit destruction of one or more cusps leaving ragged portions attached at the commissures, or the cusp may be perforated by the rupture of a

mycotic aneurysm. The latter is seen as a thin, globular, cystic dilatation, 4 to 10 mm. in diameter, projecting from the ventricular surface of the cusp and opening into the sinus of Valsalva. The mitral and tricuspid valves may be similarly involved, showing loss of substance and rupture of chordae tendineae. The left side of the heart is most frequently affected as in the subacute type, although there is some difference in the incidence of involvement of individual valves. While the mitral is

the pneumococcus, staphylococcus, and gonococcus. The tricuspid is most often attacked by hemolytic streptococci and gonococci.

Complications.—Although acute bacterial endocarditis is itself a complication of some previous infection, there are complications which result from the valvular infection as well. These, in general, are the same as those for the subacute type with some exceptions. Petechiae, visceral infections from vegetative emboli, and embolic nephritis are fairly common as may be

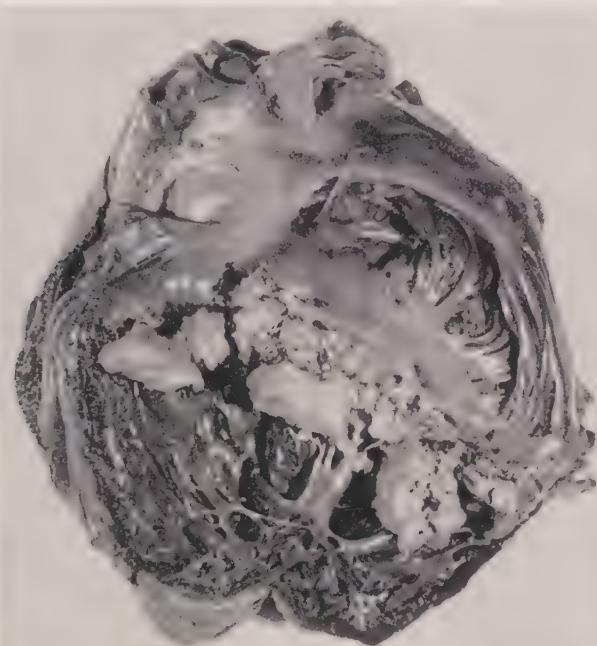


Fig. 360.—Acute bacterial endocarditis of the tricuspid valve (*Staphylococcus aureus*). Abscess of testicle with scrotal fistula. Negro, aged 56 years.

most frequently affected in subacute bacterial endocarditis and in the acute form due to the hemolytic streptococcus, the aortic valve is most often the seat of vegetations in acute infections caused by

seen in Table VI.⁸⁶ Secondary anemia and cardiac failure are important manifestations. Severe hemorrhages occur as they do in any acute fulminating infection. These may be purpuras, or bleeding from the nose, mouth, lungs, or gastrointestinal tract.

RECOVERY RATE IN SUBACUTE BACTERIAL ENDOCARDITIS

	CASES NO.	RECOVERIES NO.	PER CENT
<i>Presulfonamide era</i>			
Libman (1925)	150	4	2.7
Collected series (Lichtman)	2,596	25	1.0
<i>Sulfonamide era</i>			
Collected series (Lichtman)	659	32	4.9
<i>Penicillin era (1944-)</i>			
Collected series (1948-1950)	661	417	63.1
Friedberg's series	148	98	66.2

The prognosis in bacterial endocarditis has been decidedly gloomy in the past. The accompanying table from Friedberg⁹⁰ shows how the prognosis has changed for the better in recent years.

OTHER TYPES OF ENDOCARDITIS

Nonbacterial Thrombotic Endocarditis.—This condition is often called *terminal* or *cachectic endocarditis* and belongs to the group that Libman⁹¹ has designated indeterminate endocarditis. By indeterminate is meant a group in which

The *valvular* lesions vary in form from pin-head-sized, grayish or yellowish verrucae seen along the closing edge of the valve, resembling closely those of acute rheumatic endocarditis, to small papillary excrescences attached to the nodes of Arantius or polyplike, pedunculated growths arising often from valve surfaces. Occasionally, larger "thrombotic" masses are present which suggest bacterial endocarditis. The lesions are confined to the cardiac valves and are apparently without clinical significance.



Fig. 361.—Atypical verrucous endocarditis of mitral and aortic valves. (Libman-Sacks.) Woman, aged 38 years. Diagnosis: Lupus erythematosus disseminatus. (Courtesy Dr. Reuben Straus.)

there is no constant clinical picture, and the position of the group is uncertain pathologically. Of the 47 examples of terminal endocarditis cited by Gross and Friedberg,⁹² 32 were in patients suffering from cachectic or infectious diseases associated with chronically deformed valves usually of rheumatic origin. Five additional examples were in cachectic patients in whom verrucae occurred on otherwise normal cardiac valves.

Atypical Verrucous Endocarditis (Libman-Sacks).—A peculiar type of endocarditis first recognized by Libman in 1911 and later described by Libman and Sacks⁹⁴ is a cardiac manifestation of a grave condition known as lupus erythematosus disseminatus (see page 1144). In cases reported,^{92, 93} the patients have ranged in age from 10½ to 48 years. Only 2 out of 15 patients were males. The symptoms are largely those of disseminated lupus with

evidence of cardiac involvement such as pericarditis or cardiac murmurs. The Libman-Sacks endocarditis is present in less than half of the lupus cases. The *endocardial lesions* consist of verrucae arranged in a single beadlike chain along the closing edge, or as separate nodules or conglomerate mulberry-like masses scattered over the valvular surfaces. They tend to be somewhat larger than the verrucae of acute rheumatic endocarditis. (Fig. 361.) The color varies from gray to tawny yellow. All of the valves are attacked including also the auricular and ventricular mural endocardium. The mitral and tricuspid valves are most frequently involved. Although the lesions may occur at times along the closing edges of the valves, they frequently are found on the expanded surfaces of the leaflets or may cover the undersurface of the valve filling the mitral pocket. Blood cultures are quite uniformly negative and embolic lesions are absent.⁹⁵

Tuberculous Endocarditis.—Tuberculous endocarditis is for the most part a lesion of minor significance, occurring usually in the form of miliary tubercles on the valves or the mural endocardium as part of a generalized miliary tuberculosis.⁹⁶

Other Granulomatous Forms of Endocarditis.—Vegetative endocarditis caused by higher bacteria, yeasts, and fungi has been reported relatively frequently in recent years. *Actinomycosis* occasionally attacks the heart but only infrequently the cardiac valves. Of 68 cases of actinomycosis of the heart reviewed recently by Cornell and Shookhoff,⁹⁷ 24 involved the endocardium. Valvular endocarditis was present, however, in only 5 instances. The disease course resembles that of subacute bacterial endocarditis.

Five cases of subacute endocarditis due to *Monilia albicans* were reported between 1939 and 1942.⁹⁸ Endocarditis due to a yeastlike fungus, *Histoplasma capsulatum*, has been reported.^{98, 99} Several cases of *Erysipelothrix* endocarditis have appeared in the literature.^{100, 101}

LESIONS OF THE MYOCARDIUM

Degenerations

Parenchymatous Degeneration.—Parenchymatous degeneration and *cloudy swelling* are terms applied to the gross appearance of the myocardium. The cardiac muscle is usually soft and flabby, and the ventricles are likely to show some dilatation. On the cut surface the muscle of the left ventricle has a characteristic swollen, opaque, gray or grayish-brown appearance. The translucency of the normal muscle is replaced by a frosted-glass appearance due to innumerable small protein particles present in the muscle fibers. In the living patient, parenchymatous degeneration is reversible or it may progress to a state of fatty degeneration. Cloudy swelling accompanies not only the high fever of the infectious diseases (lobar pneumonia, diphtheria, scarlet and typhoid fevers), but also intoxications due to metallic poisons such as mercury and copper. Postmortem autolysis produces changes which are similar to cloudy swelling.

Fatty Degeneration.—Fatty degeneration is commonly the next step in the degenerative process. A number of agents, however, tend to produce fatty change independently of any parenchymatous degeneration. Highly refractile granules and droplets of fat appear in the muscle fibers, at first sparsely placed but later more abundantly. Finally, complete obliteration of cross striations and nuclei occurs.¹⁰² Zigzag yellow lines are seen on the trabeculae and papillary muscles particularly of the left ventricle, the so-called "tigering." The heart muscle appears gray or pale yellow in color and soft and flabby in consistency.¹⁰³

Severe anemias causing anoxia of the myocardium are important causes of fatty degeneration. Among the blood changes, pernicious and aplastic anemias are found frequently. At times, leukemia is responsible. Severe loss of blood or coronary insufficiency may act in a similar way. Other causes are infectious diseases (diphtheria, scarlet fever, and other bacterial toxemias), high fever lasting several weeks, poisoning by phosphorus, arsenic, chloroform, ether, alcohol, or poisonous fungi. The myocardium is not greatly weakened in fatty degeneration as a rule, but in severe degrees it may be the cause of cardiac failure. On the other hand, this condition may represent the final stage in failure of the heart to compensate.

Fatty infiltration of the myocardium pertains primarily to infiltration of epicardial fat into the interstitial connective tissue of the right ventricle. As the interstitial fat increases in amount, the adjacent muscle fibers tend to atrophy. In severe instances the greater part of the muscle may give place to fat. Marked dyspnea is present on exertion and occasionally the condition is responsible for sudden right ventricular failure if the heart is overtaxed. Fatty infiltration develops usually in older persons who are obese and who are physically inactive. It is more common in women.

Brown Atrophy.—Brown atrophy of the heart occurs in severe inanition or starvation and in chronic wasting diseases such as pulmonary tuberculosis, cancer, and chronic sepsis. While the effect is greater in elderly persons, it occurs in young adults as well. The heart is greatly decreased in size and is distinctly brown in color.

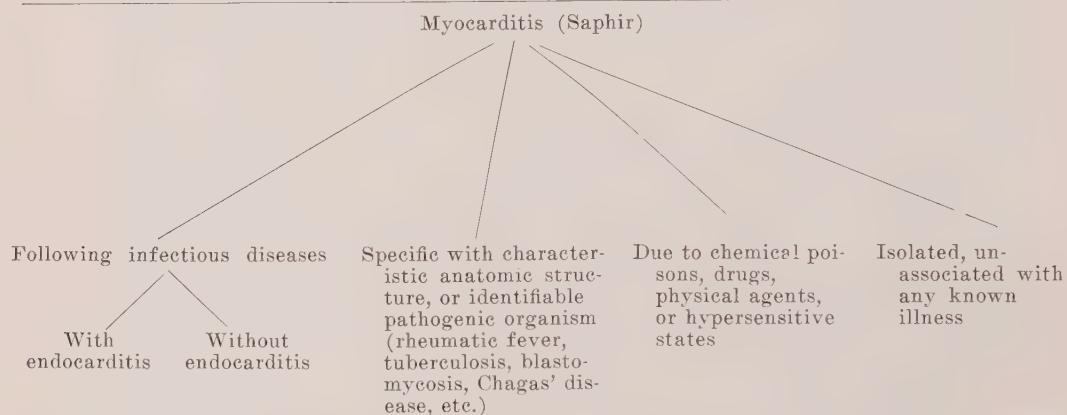
Glycogen Infiltration (von Gierke's Disease).—In von Gierke's original description the liver and kidneys were enlarged due to glycogen infiltration (hepatomegaly) but the heart was not involved. Glycogen accumulations in the myocardium seem to be a particular type of glycogen storage disease since other organs are usually not involved¹⁰⁴ (see also page 70).

Fragmentation of the Heart Muscle.—Soft, flabby hearts seen at autopsy may show on microscopic examination cross fractures of almost every fiber in one or more places. Conditions in which fragmentation may be found are advanced age, chronic sepsis, circulatory failure, and violent death (hanging, drowning, etc.). Fracture of the muscle fibers is believed to occur during the agonal state preceding death since no clinical significance has been demonstrated.

Myocarditis

The apparent statistical incidence of myocarditis has undergone profound change in the last twenty years. In the past, almost every elderly patient died of "chronic myocarditis," which, in reality, consisted of scars in the muscle or healed infarcts. Today, "myocarditis" is used more frequently to designate the much less common inflammatory changes in the heart muscle. Following is Saphir's^{105, 106} classification of myocarditis.

stages, followed by perivascular leukocytic infiltration of the supporting tissue. This is usually patchy but in more severe cases becomes quite diffuse. Varying degrees of degeneration and necrosis of the muscle fibers are associated with the interstitial inflammation¹⁰⁷ (Fig. 362). Experimental studies indicate that the toxin is responsible for the cardiac changes in diphtheria.¹⁰⁸ **Abscesses** occur in the myocardium rather infrequently. These are observed in cases of pyemia, as metastatic phenomena in other instances of over-



Myocarditis of Acute Infectious Diseases.—The changes may be toxic, affecting chiefly the muscle fibers (cloudy swelling, fatty degeneration, and necrosis), or inflammatory, involving chiefly the interstitial connective tissue. In the early stages of severe infections (diphtheria, typhoid, pneumonia, etc.), degenerative processes, including necrosis, are likely to be prominent, while in other instances inflammation of the supporting tissue with infiltration of lymphocytes, plasma cells, eosinophiles and Anitschkow myocytes may be predominant. Often the two processes are associated. In lobar pneumonia parenchymatous degeneration of the myocardium is found, often with some fatty degeneration. Inflammatory changes occur in only about 3 per cent of cases.¹⁰⁵ Grossly, the heart may show in the majority of cases of **diphtheritic myocarditis** nothing more than slight loss of tone, while in severe instances the muscle is flabby, friable, and pale. Microscopically, progressive, interstitial edema and congestion are seen in the early

whelming sepsis, and sometimes in subacute bacterial endocarditis. *Staph. aureus* is the infecting organism in the majority of cases (Fig. 363). *Pneumococci*, *Str. viridans*, *Str. pyogenes*, *meningococci*, and other pyogenic organisms are more rarely present. Rarely, abscesses develop in the myocardium as the result of certain fungous infections, viz., actinomycosis and blastomycosis.^{109, 110} Myocarditis is frequently seen in certain viral and rickettsial diseases.¹¹⁷ It is uniformly present in scrub typhus (Tsutsugamushi group) and occurs in about 50 per cent of the cases of epidemic typhus and Rocky Mountain spotted fever.^{106, 111} (Fig. 364.) "Typhus nodules" may occur in the skin, brain, heart, and other organs. They are rounded collections of lymphocytes and plasma cells usually associated with a small vessel. They are more often seen in epidemic typhus (see pages 302 and 303).¹¹²

Myocarditis Due to Chemical Poisons, Drugs, Physical Agents, etc.—Myocardial changes secondary to intoxications, physical agents, and hypersensitive states are included here. Acute

or chronic poisoning with illuminating gas and carbon monoxide produce perivascular hemorrhages and focal necroses in the brain and myocardium (see page 146). Areas of predilection in the heart are the papillary muscles of the mitral valve and the wall of the left ventricle.^{113, 114} The bundle of His may be involved with partial or complete heart block. Haggard¹¹⁵ was able to produce complete heart block in dogs as a result of exposure to carbon monoxide gas plus the anoxemia of respiratory failure. Inhalation of carbon dioxide and oxygen restored conduction to normal. The cardiac and cerebral lesions of carbon monoxide poisoning are primarily vascular. Coronary thrombosis develops fairly frequently and may occur in otherwise normal vessels.¹¹³ The author has recently seen a severe myocarditis in a young woman who died of chronic arsenic poisoning (Fig. 365).

Although not a well-established entity, there is evidence that sulfonamide therapy tends to produce in some patients an interstitial myocarditis characterized by infiltration with eosinophiles,^{116, 117, 118} Fawcett,¹¹⁹ however, in a well-controlled series of cases failed to find any increase of interstitial myocarditis in patients who received sulfonamide therapy.

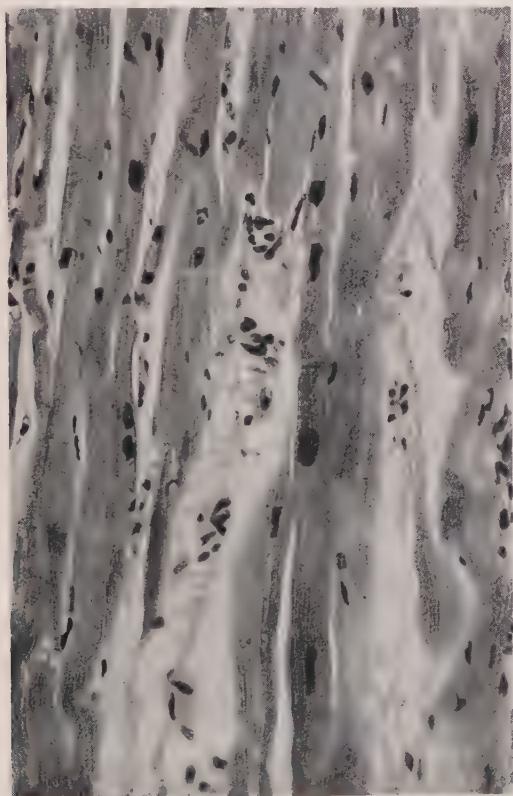


Fig. 362.—Acute diphtheritic myocarditis in a 17-year-old white girl who died in complete heart block on the fourth day of illness. Note edema, swelling of muscle fibers, loss of cross striations, and early hyalinization. A few large mononuclear cells are present.

Isolated Myocarditis (Fiedler's¹²⁰ Myocarditis; Acute Interstitial Myocarditis).—As the term indicates, this is an "isolated" or primary myocarditis which occurs without the usual apparent cause, viz., endocarditis, acute infectious disease, etc. There is often rapidly progressive



Fig. 363.—Pyemic abscesses in myocardium. (*Staphylococcus aureus*.)

myocardial failure or sudden death. The condition is not a specific disease but probably the result of a wide variety of factors. There are two distinct kinds, (a) the *diffuse* type, and (b) the *granulomatous* type. The diffuse form is encountered more frequently than is the granulomatous type. It is characterized by diffuse infiltrations of lymphocytes and plasma cells, mononuclear cells, eosinophiles, and a few polymorphonuclear leukocytes. Variability of the lesion is emphasized, culminating in extensive fibrosis. Multinucleate giant cells of myogenic origin may be found without the formation of a granuloma. The granulomatous form develops nodules resembling small tubercles or gummas. Since tuberculosis and syphilis are occasionally associated with this form of the disease, there is a tendency to regard these infections as etiological factors, regardless of the fact that neither tubercle bacilli nor spirochetes have been found in the lesions. Microscopically, well-developed granulomas are present with necrosis.¹⁰⁵

Myocarditis Associated With Bacterial Endocarditis.—No distinctive type of myocarditis is associated with bacterial endocarditis. A variety of processes have been described as occurring from time to time. Petechial hemorrhages may be present in the myocardium as elsewhere. Small foci of necrosis as well as small abscesses are commonly observed. The latter are probably the result of bacterial emboli. Polymorphonuclear leukocytic infiltration and to a lesser degree lymphocytic infiltrations are seen in the interstitial tissue. Organizing infarcts are the lesions most frequently ob-



Fig. 364.—Myocarditis in scrub typhus.

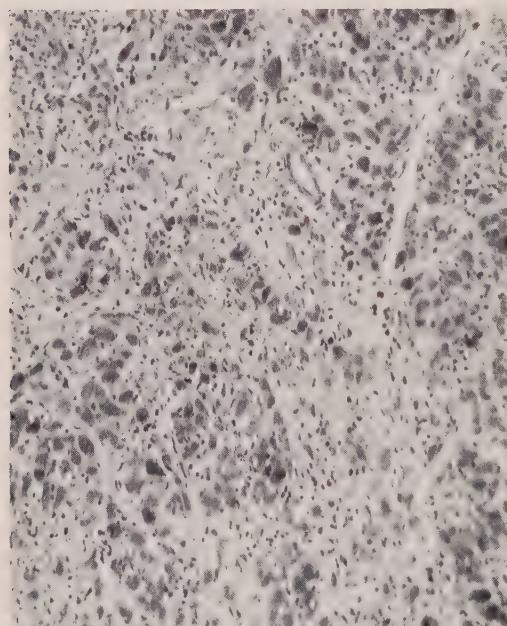


Fig. 365.—Myocarditis in chronic arsenic poisoning in white woman, 27 years old. Main coronary arteries normal. Note loss of muscle substance, edema, and cellular infiltration.

served.¹²¹ Bracht-Wächter bodies are interpreted as foci of lymphocytes found in the muscle fibers in areas where the fibers have undergone necrosis.¹²² Other authors describe these lesions differently. Since there is no agreement as to the exact interpretation of these bodies, Saphir¹⁰⁵ suggests the term be dropped. Aschoff bodies may be present in the myocardium since rheumatic endocarditis is frequently a predisposing factor. Anitschkow myocytes are found in increased numbers in many instances.

SPECIFIC MYOCARDITIDES

Rheumatic Myocarditis.—See page 453.

Syphilitic Myocarditis.—In syphilitic myocarditis, gummata may occur in the myocardium. These may involve the epicardium and produce pericarditis or may break into one or more chambers of the heart. Gummatous myocarditis refers to small lesions occurring locally or scattered diffusely through the myocardium.¹²³ There is general agreement among pathologists up to this point. Whether or not an entity exists known as "diffuse syphilitic myocarditis," consisting of an inflammation comparable to other fibrosing lesions in acquired syphilis, with spirochetes present, is highly controversial. Warthin¹²⁴ was the advocate of this idea a generation ago. Today, most students of the subject agree that such an entity either does not exist or is, at least, exceedingly rare.

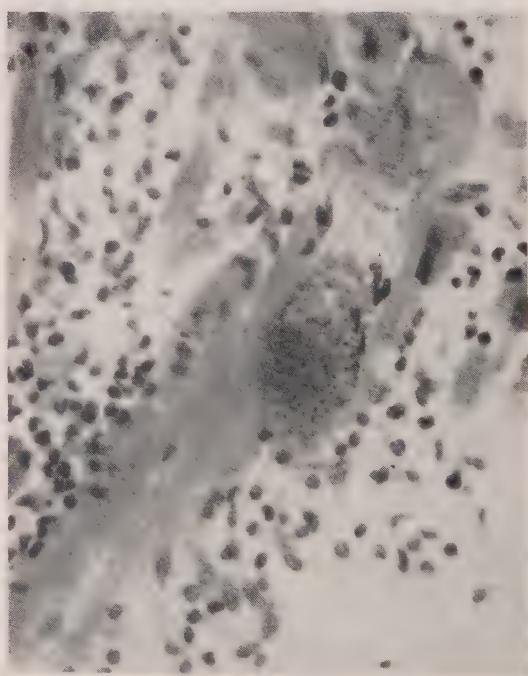


Fig. 366.—Myocarditis in Chagas' disease. Note loss of muscle substance and heavy infiltration with lymphocytes, plasma cells, and macrophages. Near the center is a cystlike structure containing many Leishmania forms of *Trypanosoma cruzi*.

Tuberculous Myocarditis.—Tuberculosis of the myocardium is a rare condition, only about 200 cases having been reported in the literature.^{125, 126}

MYOCARDITIS CAUSED BY PARASITES

Myocarditis in Chagas' Disease.—Chagas' disease is due to infection with *Trypanosoma cruzi*. Practically any organ of the body may be invaded, but the myocardium, skeletal muscle, and central nervous system are most frequently attacked. The cardiac muscle is invaded by trypanosomes, usually in childhood, and this leads to cardiac weakness and failure.^{129, 130} (See discussion on page 364.)

after infection. Microscopically, both parenchyma and interstitial tissues are involved. Focal necrosis is frequently seen. The inflammatory cells are predominantly lymphocytes though eosinophiles are present in some instances (see discussion on page 401).

Echinococcus cyst and *cysticercus cellulosae* may involve the heart, although rarely.¹³⁵

FOREIGN BODIES IN THE HEART

Foreign bodies may enter the myocardium or the chambers of the heart and remain for years with little effect. Projectiles, shrapnel, and bullets, especially in times of war, are the ob-

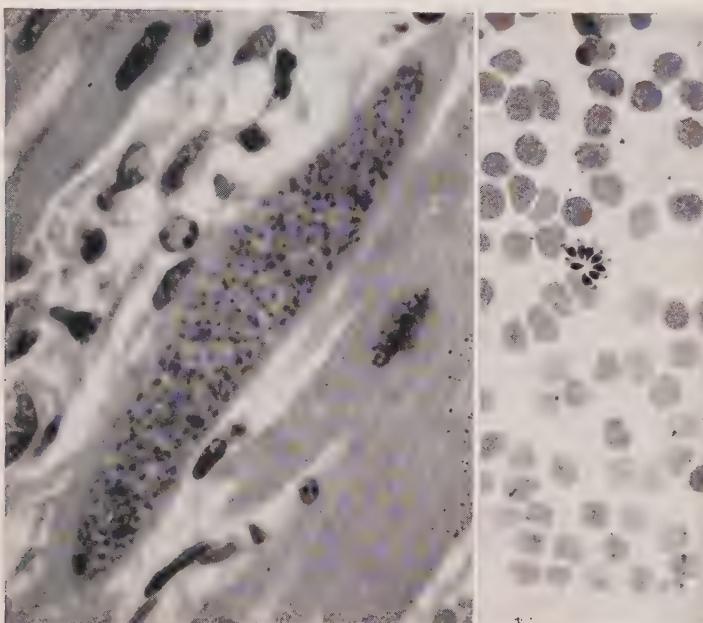


Fig. 367.—Toxoplasmosis. Toxoplasma in human heart muscle (left), and in smear from omentum of guinea pig (right). (From Pinkerton, H., and Henderson, R. G.: J. A. M. A. 116: 807, 1941.)

Myocarditis in Toxoplasmosis.—Human toxoplasmosis was first reported in adults by Pinkerton and Weinman (1940).¹³¹ The disease which is caused by a protozoan is similar in its clinical and pathologic manifestations to certain rickettsial diseases (Rocky Mountain spotted fever and endemic typhus). In the first case described involving the myocardium, there were deposits of fibrin, areas of focal necrosis, and heavy infiltrations of polymorphonuclear and eosinophilic leukocytes. Large mononuclear cells were observed at the periphery of the lesion. In two later cases,¹³² fusiform collections of Toxoplasma organisms were found within or between the muscle fibers but with only slight inflammatory reaction in the myocardium. (Fig. 367.)

Intestinal Parasites Which Affect the Heart.—

TRICHINOSIS.—Although rare, myocarditis does occur in infections with *Trichinella spiralis*.^{133, 134} Death from this type of myocardial disease usually occurs between the fourth and sixth weeks

objects most frequently found lodged in the heart. Needles entering the soft parts almost anywhere may eventually reach the heart. Objects within the chambers of the heart may migrate to the femoral or iliac arteries. Such an instance was seen at the Los Angeles County Hospital. A 22-caliber bullet had entered the left ventricle of a young boy without fatal consequences. Before surgery was undertaken he developed a severe pain in one leg. The bullet had migrated to the popliteal artery where it was removed without difficulty.

TRAUMA TO THE HEART

Until recently only penetrating wounds of the heart were given serious consideration. Beck¹³⁶ (1935) called attention to a group of nonpenetrating injuries resulting in contusions of the myocardium. Penetrating wounds of the heart are due to such obvious causes as gunshot, shell fragments, and bayonet injuries suffered promi-

nently in times of war. Knife, dagger, and gunshot wounds are, likewise, not infrequently seen in the emergency hospitals and morgues of our larger cities in times of relative peace. If the wound perforates the myocardium, cardiac tamponade occurs, producing death within a few minutes.¹³⁶ Nonpenetrating wounds of the heart may be due to direct or indirect injuries of the heart. A direct blow over the precordium may fracture the sternum and several ribs. If the heart is penetrated, death is immediate. If the myocardium is bruised, several outcomes are possible: viz., There may be delayed rupture, cardiac failure may intervene without rupture, an aneurysm of the heart may develop, or the patient may recover completely. The heart may suffer contusion or compression by being caught between the sternum and vertebrae. The common "steering wheel" accidents are of this type. Indirect forces are applied to the heart and great vessels by sudden compression of the legs and abdomen. A man suddenly engulfed in a sandbank to his waist died immediately from rupture of the heart and pericardium.¹³⁷ In another case, a laborer 40 years of age was caught in a cave-in of earth which knocked him down and covered his legs and thighs. His sudden death was due to a ruptured aortic arch, rupture of several mesenteric vessels, and fracture of the liver.¹³⁸ These are examples of cardiac or vascular rupture due to sudden compression of a considerable part of the vascular bed, thus driving a noncompressible fluid (blood) into the heart or great vessels which are already filled with blood.¹³⁹ The following statistics are illuminating: of 175 patients suffering nonpenetrating wounds of the heart, 152 (87 per cent) died of cardiac rupture; 11 (6 per cent) died of cardiac failure; while 12 patients (7 per cent) recovered.¹³⁹

Circulatory Disturbances of the Myocardium

Just as heart disease is the leading cause of death, *coronary artery disease* is the chief cause of death in adult patients with organic heart disease. About 50 per cent of these patients suffer from hypertension, but the immediate cause of death is coronary occlusion with acute myocardial infarction.

ANATOMY OF THE CORONARY CIRCULATION

There are two main coronary arteries, (1) the left anterior descending and (2) the right coronary. The *left coronary artery* arises from the aorta opposite the left posterior sinus of Valsalva, runs forward between the pulmonary artery and the left auricle, and soon divides into anterior descending and circumflex branches. The anterior descending artery passes down the anterior interventricular sulcus to the apex and generally extends around to the posterior surface, supplying the posterior apical portion of both ventricles. Approximately the anterior one-third of the right ventricle is supplied by small accessory branches from the anterior descending coronary. Similar but larger acces-

sory branches are given off on the left to supply the anterior wall of the left ventricle (Fig. 368).

The *left circumflex branch* arises near the base of the ventricle and courses to the left in the coronary sulcus. As a rule, it passes around the obtuse or left margin of the heart, where it leaves the coronary sulcus to supply the left third to left half of the posterior basal portion of the left ventricle. Thus, in the average normal heart, the left coronary artery supplies the entire anterior surface of the left ventricle, the adjacent third of the anterior part of the right ventricle, the apex of both ventricles, the anterior two-thirds of the interventricular septum, all of the apical part of the septum and the left half of the posterior surface of the left ventricle.

The *right coronary* arises near the upper border of the anterior sinus of Valsalva and passes downward and to the right in the coronary sulcus, where branches are given off to supply the anterior surface of the right ventricle. A fairly large *right marginal artery* is given off at the right margin in addition to several smaller descending branches. A large *posterior descending branch* passes downward along the posterior interventricular sulcus, gives off branches to and finally enters the septum. The right coronary artery usually continues along the coronary sulcus where descending branches go to supply the posterior part of the left ventricle. The right coronary, therefore, supplies two-thirds of the anterior surface and all of the posterior surface of the right ventricle except the apex. It usually supplies the posterior one-third of the interventricular septum (except the apex) and the basal three-fifths of the posterior surface of the left ventricle.^{140, 141}

There are two chief variations in the distribution of the coronary arteries. In 8 to 10 per cent of cases the left circumflex artery is larger than usual, extending along the coronary sulcus across the entire anterior and posterior surfaces of the left ventricle to reach the posterior interventricular septum where it turns downward to become the posterior descending artery. Under such conditions the entire left ventricle and all of the interventricular septum are supplied by the left coronary. The right coronary artery is small under these circumstances. In a somewhat greater percentage of instances the opposite condition is true: The right coronary is large, taking over some of the territory usually supplied by the left circumflex. The right coronary may supply all of the posterior wall and in some cases part of the anterior wall of the left ventricle. Whitten¹⁴⁰ describes a difference in the method of coronary branching in the two ventricles. In the thicker left ventricle the smaller branches arise from the main arteries near the epicardium and give off smaller branches which penetrate the muscle forming arborizations as they approach the endocardium. In the right ventricle the branches are given off in the same plane in which the larger arteries lie.

The coronary arteries are essentially arterioles of muscular type but they undergo arteriosclerotic changes in a manner similar to that seen in the aorta. Furthermore, normal coro-

nary arteries have thick intimal coats as compared with arteries of similar caliber seen elsewhere. This is presumably a response to the relatively high pressure in these vessels. Dock¹⁴² has reported intimal thickenings in the coronary arteries of newborn infants, averaging 26 per

coronary arteries of 35 infants ranging from prematures to 1 year of age. He found that the intimal thickenings are confined to points of branching, tapering off immediately above and below these levels. Anastomoses are present between the right and left coronary branches as

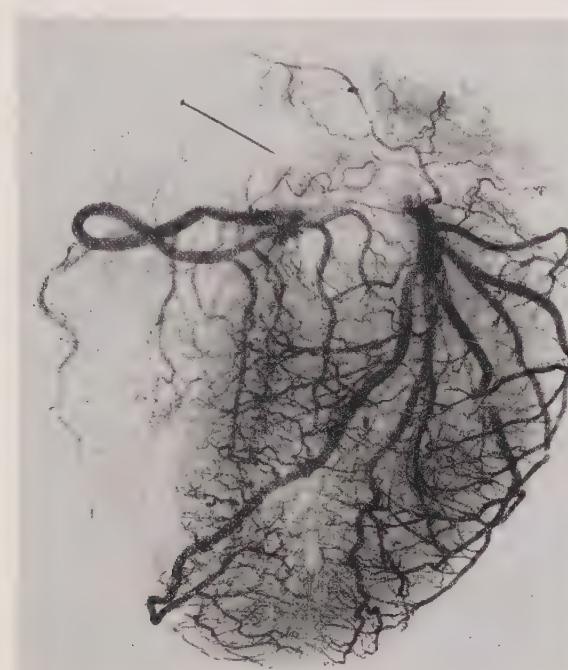


Fig. 368.—Roentgenogram of injected coronary circulation in a normal adult heart. (From Gross: *The Blood Supply to the Heart*, Paul B. Hoeber, Inc.)

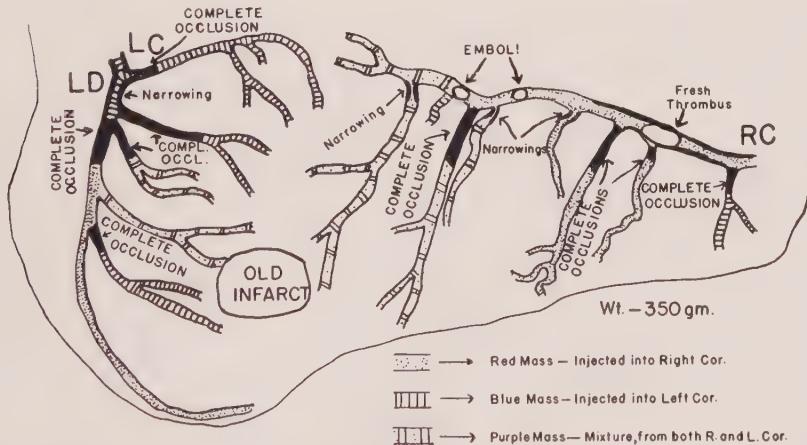


Fig. 369.—Diagram of coronary circulation following lead-agar injection showing multiple complete occlusions. (From Blumgart, Schlesinger, and Davis, *Am. Heart J.*, 1940.)

cent of the thickness of the media in males and 8 per cent in females. This idea has been supported more recently by Fangman and Hellwig.¹⁴³ However, Lack,¹⁴⁴ working in our laboratory, has examined by serial sections the

shown by dye studies. Prinzmetal and co-workers¹⁴⁵ using minute glass spherules suspended in a radiopaque mixture, found the anastomoses in normal hearts to vary from 70 to 180 microns.

CORONARY OCCLUSION

Coronary artery disturbance is usually due to some form of occlusion. The syndrome referred to as "coronary occlusion," which consists of severe, prolonged substernal pain, a fall in blood pressure, pallor, and other evidences of shock, accompanied by changes in the electrocardiograph and by fever, leukocytosis, and an increased sedimentation rate, actually signifies myocardial infarction and should be so designated.^{146, 147} By means of lead-agar injection of the coronary arteries by the Schlesinger¹⁴⁸ technique, many complete occlusions have been demonstrated in the absence of significant pathologic or clinical evidence of myocardial damage. The apparent inconsistency of such findings is explained by the presence of large anastomoses which by-pass the obstructed area.¹⁴⁷ More than 50 per cent of the occlusions of the coronary arteries are overlooked in ordinary postmortem dissections (Fig. 369). Women are less prone than men to experience coronary artery disease and tend to develop it at a later age.¹⁴⁹

Etiology of Coronary Occlusion.—

PREDISPOSING FACTORS.—Until quite recently, disease of the coronary arteries was considered a disease of old age. It is no longer rare to observe men under 40 who have fallen victims to this disease.¹⁵⁰ Hypertension is present in many patients suffering from coronary artery disease. Heredity is important, and disease of the coronary arteries tends to be familial. City dwellers are more prone to develop coronary disease than are their country cousins.¹⁵⁰ Conclusive data on the effects of diet are not available. There is evidence that a high fat diet tends to increase coronary sclerosis regardless of the cholesterol content.¹⁵¹ Gofman and associates¹⁵² have shown that lipoproteins of low density, but in the form of large molecular aggregates are two to three times more numerous in the serum of persons who have had myocardial infarcts and are therefore presumably atherosclerotic than in the serum of a control group (persons without evidence of atherosclerosis). Cholesterol is relatively low in the serum lipids at these levels. (See page 519 for further discussion.)

It is generally believed that overweight is an important predisposing cause of coronary artery disease. However, Yater and co-workers¹⁵³ failed to find any significant overweight in their group of 450 young soldiers (18 to 39 years) who died of coronary artery disease during World War II. There was slight overweight in the group of men 50 years and older. Overweight is important if there is some cardiac impairment as indicated by tachycardia or elevated blood pressure. Diabetics exhibit a

higher percentage of coronary artery disease than nondiabetics of the same age group.¹⁵⁴ The use of tobacco may be of importance in predisposing to coronary disease, although definite evidence is difficult to obtain. Yater and associates¹⁵³ found no significant difference between their group of young soldiers with coronary artery disease and the control group as regards the use of tobacco and alcohol. This does not mean necessarily that the same is true for the older age group, say from 40 to 59 years, in regard to tobacco since an additional 5 to 15 years of smoking may well have a detrimental effect not seen in younger persons. There is little evidence that alcohol affects the coronary circulation adversely.

Acute hemorrhage such as may occur from a bleeding duodenal ulcer tends to precipitate attacks of acute coronary insufficiency. This has grave significance for patients in whom the coronary circulation is already impaired.¹⁵⁵

Many factors predisposing to coronary artery disease are also factors tending to produce general arteriosclerosis since this process is fundamental in lesions of the coronary arteries (see page 520).

Coronary Sclerosis.—Arteriosclerosis of the coronary arteries is the basic lesion in most instances of coronary occlusion. The process follows closely that seen in the aorta. In some persons the atheromatous plaques, consisting of cholesterol with its esters, neutral fat, and necrotic debris, tend to remain soft. In patients of advanced years, calcification is usually present, often to an extreme degree. Deposition of calcium most often begins in the fibrous tissue adjacent to the atheroma. If the arteriosclerotic plaque remains soft it may rupture, allowing the soft contents to occlude the lumen of the artery either locally or distally. (Fig. 372.) The anterior descending branch of the left coronary is the vessel most frequently sclerosed. The area of severest involvement begins about 3 cm. from the aorta. The right coronary is almost as frequently involved as the left, the segment of greatest degenerative change occurring at about the same distance from the aorta, viz., 3 to 4 cm.¹⁵⁶ The effects produced depend in a broad sense on the rate at which the coronary arteries become narrowed. If the arteriosclerotic process develops gradually anastomoses already present dilate and new channels are opened up. Anastomoses develop readily about areas of arteriosclerotic narrowing or occlusion and are not dependent on age as was formerly believed.¹⁴⁸ Arteriosclerotic narrowing of

larger branches with occasional occlusions produce anastomoses 200 microns or more in diameter. The larger caliber anastomoses are important in the nourishment of the muscle following an occlusion. There may be sufficient of these to prevent infarction even when both main coronary

arteries are occluded.¹⁴⁶ If a main vessel is narrowed rapidly or a sudden occlusion develops, there is insufficient time for adequate anastomotic channels to develop and infarction results. Coronary sclerosis may produce symptoms of coronary failure in comparatively young

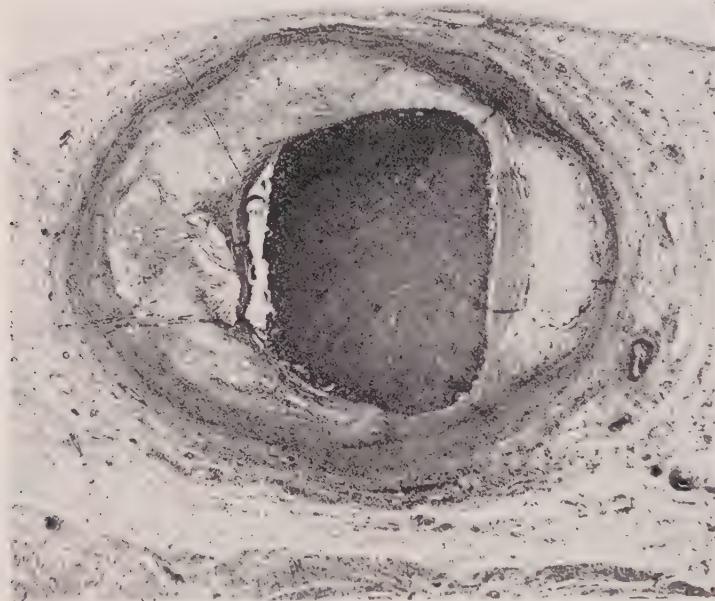


Fig. 370.—Coronary sclerosis and thrombosis. The intima is irregularly thickened and the media thinned because of advanced atheromatosis.

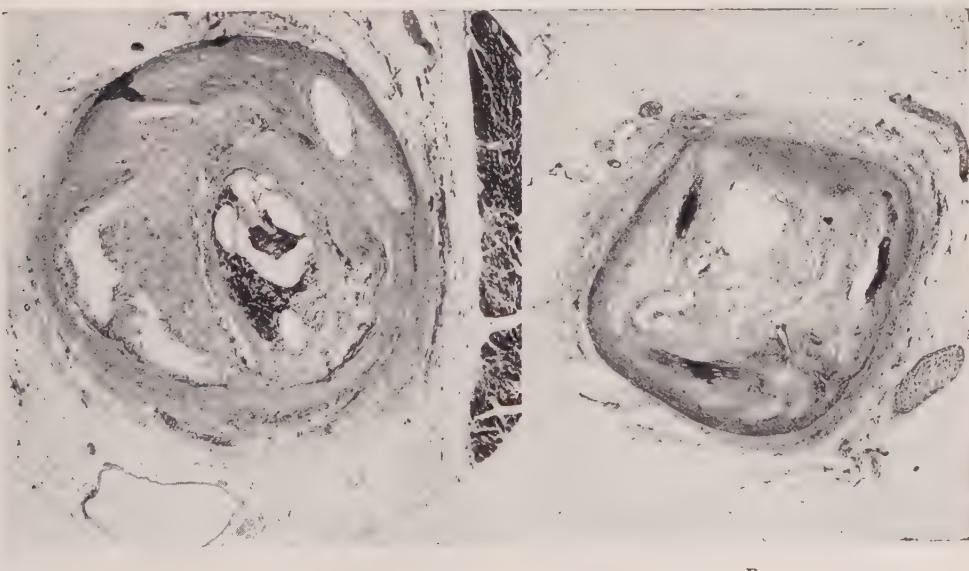


Fig. 371.—A, Organization and recanalization of a thrombosed coronary artery. Note extreme atheromatous degeneration. The dark central masses consist of old fibrin. Man, aged 43 years. Left circumflex branch. B, Right coronary artery from the same patient.

persons (20 to 40 years) but it is much more common after 50 years of age.

Coronary Thrombosis.—Thrombosis in the majority of instances occludes arteries already damaged by arteriosclerosis but is confined, as a rule, to the larger

arterial thrombi that have become organized and thus transformed into fibrous intimal plaques. If myocardial infarction occurs due to thrombosis and the patient survives, the infarct becomes organized. The coronary thrombus may organize but fail to recanalize, apparently because of the small amount of blood required by the infarcted area.

Intramural Hemorrhage.—Hemorrhage into the wall of a coronary artery may be subintimal and may rupture into the lumen of the arteriosclerotic vessel. Occasionally, a subintimal hematoma may be sufficiently large to practically close the lumen without rupturing into it.¹⁵⁹ Hemorrhages may arise in the deeper parts of the thickened intima from small vascularized areas which accompany the atheromatous "abscesses." Such vascularized areas arise from the *vasa vasorum* or, less frequently, from capillary vessels that pass through the intima from the lumen.^{159, 160} These deeper hemorrhages usually break into an atheromatous necrotic area where the tissues are poorly supported, or they may destroy the looser and more cellular parts of the intima and thus reach the lumen. Wartman¹⁶⁰ regards intramural coronary arterial hemorrhage as second only to thrombosis in producing coronary occlusion.

Rupture of an atheromatous plaque into the lumen of a coronary artery occurs not infrequently. It occurs, usually, in the older age groups and much more often than was supposed in the past. In a coronary artery with two-thirds of the lumen obliterated by an atheromatous plaque, rupture of the intimal membrane



Fig. 372.—Ruptured atheromatous plaque producing acute coronary occlusion. White man, aged 64 years.

branches.¹⁵⁷ Coronary arteries undergoing atheromatous degeneration and calcification may lose their smooth endothelial lining and so expose a roughened area suitable for platelet deposition. The narrow opening furthermore tends to obstruct the blood stream, which probably favors thrombus formation. Acute infections or shock following an accident or a surgical operation favor coronary thrombosis (Fig. 370). If the patient survives for several weeks, organization of the thrombus ensues, followed usually by recanalization. Although the vessel is further narrowed by the fibrosing process, it is, as a rule, capable of carrying a limited quantity of blood (Fig. 371). Duguid¹⁵⁸ claims that many of the lesions classified as atherosclerotic are, in fact,



Fig. 373.—Narrowed coronary ostia in syphilitic aortitis. (See also Fig. 352.)

in a thin area may allow the pultaceous mass to occlude the lumen completely (Fig. 372).

Narrowed or Occluded Coronary Ostia Due to Syphilis.—This constitutes an important cause of coronary insufficiency (Fig. 373). It is discussed on page 460.

Coronary Embolism.—Of the major causes of coronary occlusion, embolism is the least frequent, only 45 instances having been reported up to 1945.¹⁶¹ At the Los Angeles County Hospital the ratio of coronary thrombosis to embolism was 46 to 1. Emboli may arise from mural thrombi in the left ventricle, left auricle, the left auricular appendage, and from thrombi on arteriosclerotic plaques at the root of the aorta. The pulmonary veins may become thrombosed in suppurative lesions of the lungs or due to invasion by tumor. Septic emboli may occlude the coronary arteries in bacterial endocarditis. The incidence is highest when the aortic valve is involved.¹⁶² Vegetations growing in the sinuses of Valsalva are in close proximity to the coronary ostia. Since the coronary flow is greatest during diastole when the aortic valve is closed, thrombotic material attached to the inner walls of the sinuses of Valsalva has a greater opportunity to enter the coronary ostia than emboli from within the left ventricle. It may be difficult or at times impossible to differentiate between coronary occlusions due to thrombosis and embolism. Multiple tiny emboli in cases of bacterial endocarditis may be a cause of myocardial failure.

Infrequent Causes of Coronary Occlusion.—Familial xanthomatosis is a condition occasionally responsible for coronary artery disease. Plaques composed of cholesterol and cholesterol esters may form in the main coronary arteries associated with xanthomatous lesions of skin and tendons accompanied by hypercholesterolemia. Muller,¹⁶³ 1939, reported studies on 68 persons with hereditary xanthomatosis who had some form of heart disease. There was evidence of angina pectoris in nearly all of these patients, of whom 38 had died, over one-third having died suddenly. The ages ranged from 31 to 85 years. All of the patients with heart disease had hypercholesterolemia.

Buerger's disease attacks the arteries of the extremities most frequently but occasionally involves the coronary circulation.¹⁶⁴ The diagnosis is made when coronary thrombosis occurs in males under 50 in whom circulatory disturbances of the extremities fall into the pattern of this disease. Periarteritis (polyarteritis) acuta is an uncommon disease in which fibrinous and

cellular exudation involves all coats of the arteries, resulting in occlusions and infarctions. Usually several systems or organs are attacked and the heart is no exception. Dissecting aneurysm of a coronary artery is a very rare source of occlusion. This condition is probably dependent on atheromatous changes associated with intramural hemorrhage or may extend from the aorta in dissecting aneurysm of that vessel.¹⁶⁵

MYOCARDIAL INFARCTION

The usual consequence of coronary occlusion is acute myocardial infarction. This is not invariable by any means, as the studies of Blumgart and associates^{146, 147} have shown. If occlusions develop gradually, anastomoses form which carry sufficient blood to nourish the muscle adequately in the presence of multiple complete occlusions. Conversely, acute myocardial infarcts may occur when coronary vessels are narrowed but not occluded.^{147, 165} Patients who die within twelve hours following coronary occlusion may reveal no infarct in the heart because it takes about that length of time for necrosis to become evident.¹⁶⁶

Location.—Recent infarcts of the myocardium are seen most frequently in the anterior part of the interventricular septum, extending to the anterior one-third of the lateral wall of the left ventricle, due to occlusion of the descending branch of the left coronary. The next most common site is in the posterior one-third of the septum and the posterior part of the left ventricle, due to occlusion of the right coronary. Infarcts confined to the lateral wall of the left ventricle are the result of occlusion of the left or right circumflex arteries. In each of the above exigencies the occluded artery is probably the main vessel supplying that area. The right ventricle may be infarcted, at least in part, in conjunction with occlusions of either the left or right main coronary arteries if the obstructions are sufficiently high.

Gross Appearance.—A recent infarct exhibits a purplish area with brownish mottling of the epicardium. A thin film of tawny-colored fibrin may cover the epicardial surface, except in the early stage. Most characteristic is the light brown or yellow color of the necrotic muscle when exposed by the knife. It shows the peculiar opacity of coagulated necrotic tissue. The infarcted area varies

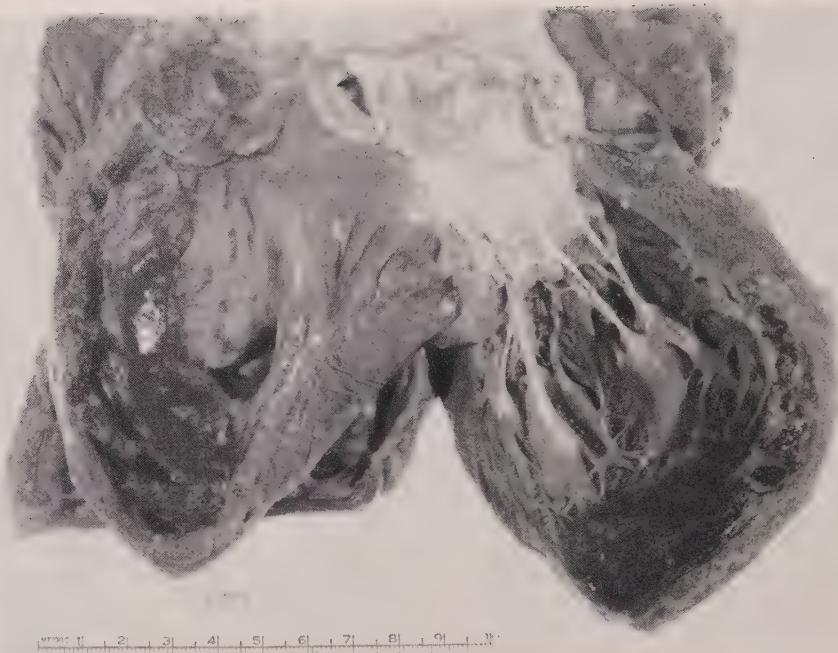


Fig. 374.—Recent myocardial infarction due to coronary thrombosis. Note lighter shade of the myocardium in central part of I.V. septum. At the lower border of the infarct is a crescentic area due to rupture of septal wall. Mural thrombosis toward apex.

in degree of friability. Patches of dark hemorrhagic discoloration are usually present, often showing best about the edges of the infarct. (Fig. 374.) *Microscopically* the infarcted area is composed of hyaline, brick-red muscle fibers (hematoxylin-eosin stain), devoid of nuclei and cross striations. Many polymorphonuclear leukocytes showing karyorrhexis may infiltrate the interstitial spaces, especially at the margins of the infarct. Some hemorrhage is nearly always present, usually most pronounced at the periphery. (Fig. 375.)

Healing.—The myocardium must continue to function following an infarction, since "obviously the heart cannot be splinted or placed in a cast as is done with traumatized muscles or bones of an extremity."¹⁶⁰ Furthermore, the blood supply to the infarcted heart muscle is obviously seriously impaired. Comparative rest for the heart may be obtained by keeping the patient in bed. The speed of healing of a given infarct depends upon its size. Small infarcts are almost completely healed in five weeks, larger ones heal in about two months.¹⁶⁶ In spite of the reduced blood supply, infarcts of the myocardium begin healing



Fig. 375.—Section from an area of acute myocardial infarction. The necrotic muscle fibers are separated by a heavy polymorphonuclear leukocytic infiltration.

promptly. The necrotic tissue is gradually removed and replaced by vascular connective tissue. Scar formation finally results as in other healing processes.

Complications.—

MURAL THROMBOSIS.—In large myocardial infarcts the endocardium is almost invariably involved, thus favoring thrombus formation. The size of the thrombus depends upon the area of endocardial

wall of the ventricle do not organize as do smaller vascular thrombi. Large ones remain in place for a considerable time even after the infarct has healed but seem to undergo gradual solution due to proteolytic enzymatic action. During this phase, mural thrombi are a constant menace since portions are likely to break away from time to time to lodge in arteries of kidney, spleen, intestine, brain, and extremities (Fig. 376).



Fig. 376.—Aneurysm of heart (interventricular septum). Note scar tissue in myocardium about the edges of the sac. A mural thrombus partly fills the aneurysm. White man, aged 81 years.

damage. In small infarcts the overlying endocardium may escape since the blood supply to the subendothelial layer may not be interrupted. Slowing of the heart and bed rest no doubt aid the formation of mural thrombi. As the infarct undergoes healing, the mural thrombus tends to soften. Thrombi attached to the inner

RUPTURE OF THE HEART.—Acute rupture of the myocardium is preponderantly the result of acute myocardial infarction. Other causes may be fatty degeneration, sepsis, or abscess formation, aneurysm, and, rarely, syphilis or tuberculosis.¹⁶⁷ Edmondson and Hoxie¹⁶⁸ found, among 25,000 autopsies at the Los Angeles

County Hospital, 865 hearts with unhealed infarcts due to coronary artery disease. There were 72 instances of spontaneous rupture; 50 (70 per cent) were on the anterior surface of the heart, while 13 (18 per cent) ruptured through the interventricular septum. These authors state that when scarring was present in the myocardium its likelihood of rupture was only one-fourth as great as in unscarred hearts. The degree of softening of the infarct and the height of the intraventricular pressure appear to be determining factors in the production of cardiac rupture. The degree of softening is

fibrous tissue and constitute relatively thin places in the wall since they are seldom more than one-third to one-half as thick as the normal left ventricle. Such scarred areas, especially if they are large, tend to bulge or stretch under the force of the systolic pressure. Since the scar tissue is not elastic it fails to recoil, and in time an old infarct may exhibit a rounded, saclike bulge in the wall of the ventricle—a so-called *aneurysm of the heart*. Such aneurysms are located in the left ventricle usually toward the apex. They occur in the areas most frequently infarcted. Mural thrombi are often

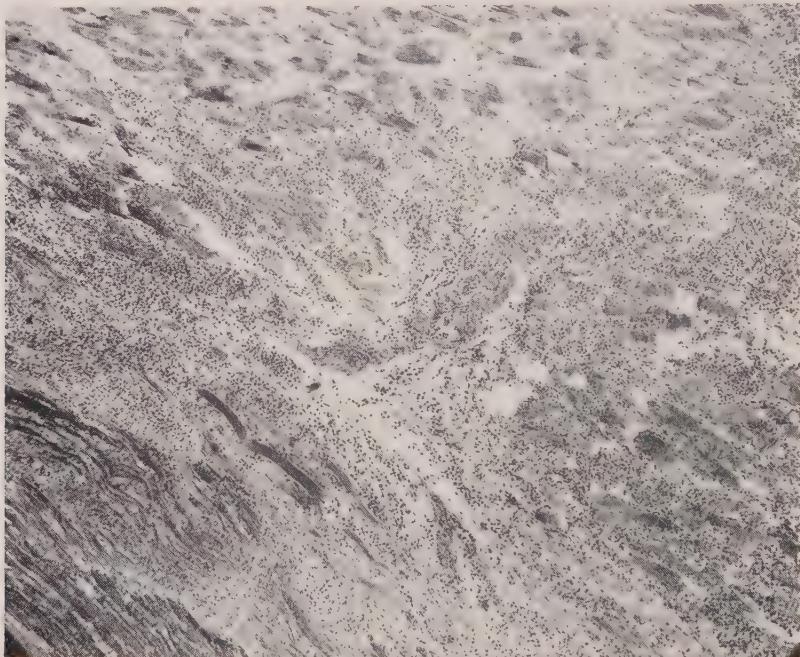


Fig. 377.—Section through ruptured myocardial infarct. Hemorrhage present among darker muscle fibers.

determined by the extent of necrosis and by the number of polymorphonuclear leukocytes present. Persons who had hypertension which persisted after onset of infarction (140 mm. Hg or above), were three times more likely to develop cardiac rupture than those with normal or subnormal blood pressures. A relatively high incidence of cardiac rupture following infarction occurs in the insane and in ambulatory individuals.

ANEURYSM OF THE HEART.—Healed infarcts of the heart are composed of

present, partly filling the sac. (Fig. 376.) Occasionally the wall of the aneurysm is calcified. The diagnosis during life is most frequently made by roentgenography.¹⁶⁹

PATHOLOGY OF SUDDEN DEATH IN CORONARY ARTERY DISEASE

The term "sudden death" is used to describe the unexpected advent of death which may have been instantaneous or may have occurred in a space of several minutes or even hours. The usual cause lies in the heart, although cerebral hemorrhage is often wrongly suspected.¹⁷⁰

Martland¹⁷¹ found in 2,000 necropsies on cases of sudden death that the most frequent anatomical lesion was coronary artery disease.

Hamman¹⁷² has summarized the important natural causes of sudden death from the reports of several authors from widely separated geographic areas. He shows that 91 per cent of such deaths are due to diseases of the cardiovascular system (heart failure, hemorrhage, arterial embolism and thrombosis). Sixty-five per cent of all cases of sudden death are due to cardiac failure and 65 per cent of these are due to coronary artery disease.

In sudden death the underlying cause is often chronic. Conditions of the heart like coronary sclerosis, cardiac hypertrophy due to arterial hypertension, aortic stenosis, and various kinds of infectious myocarditis are factors which favor syncope and predispose to instantaneous death. In these states the heart has a general tendency to asystole or to arrhythmias. Such cardiac dysfunction can be induced by stimulation of various reflexes. In the presence of coronary sclerosis, hypersensitivity of the vagal type of carotid-sinus reflex is often observed.¹⁷⁰ Ventricular fibrillation is believed to occur at least in some instances as a terminal condition.

THE PATHOLOGIC BASIS OF ANGINA PECTORIS

Angina pectoris is characterized by paroxysmal pain in the chest provoked by an increase in the demands on the heart and relieved by a decrease of the work of the heart. There is also a likelihood of termination by sudden death.¹⁷³ The physiologic mechanism in the production of this syndrome is a relative oxygen deficiency in the myocardium.¹⁷⁴ The underlying cause of ischemia of the heart muscle is usually narrowing or occlusion of one or more branches of the coronary arteries, though severe anemias may have a similar effect. Narrowing of coronary ostia due to syphilis is likewise effective. Aortic insufficiency and stenosis which reduce the coronary blood flow and at the same time increase the work of the heart also produce relative oxygen deficiency of the myocardium. Factors which increase the oxygen needs of the heart are cardiac hypertrophy (lesions of the aortic valve and hypertension), cardiac failure, and violent muscular exercise.¹⁷⁴ Blumgart and associates¹⁴⁶ found that every patient suffering primarily from angina pectoris in the absence of valvular disease or arterial hypertension has shown old complete occlusion of at least one major coronary artery at autopsy and most of them had two main coronary arteries occluded

previous to the terminal illness. The factors that tend to precipitate an attack of angina pectoris are exertion, eating, emotion, and cold, since the oxygen requirement of the myocardium is increased by each of these.¹⁷⁴

Encouraging results have been obtained by surgical treatment of patients with advanced coronary artery disease, especially those having intractable anginal pain. Vascular grafts of muscle, or fatty tissue are implanted on the heart in the hope of increasing the arterial blood supply to the myocardium.^{175, 176}

Disturbances of the Conduction System of the Myocardium

The lesions which affect the conduction system are the result of changes in the heart and the coronary circulation. These have been discussed in detail elsewhere. An exception to this is the presence of an accessory auriculoventricular pathway known as the bundle of Kent, which has been cited as the cause of the Wolff-Parkinson-White syndrome.¹⁷⁷ It is believed that impulses may pass down both pathways at once, but somewhat faster through the bundle of Kent than the bundle of His, thus producing an arrhythmia known as paroxysmal auricular tachycardia.^{178, 179} Other congenital lesions are interventricular septal defects with interruption of the auriculoventricular pathway causing complete heart block, auricular septal defects with associated auricular arrhythmias, and, rarely, disturbance due to the presence of a congenital cyst. Acute inflammatory diseases may produce lesions at various locations in the conduction system. Their effects tend to be temporary. This group includes diphtheria, staphylococcal abscesses in the myocardium, scarlet fever, bacterial endocarditis, syphilis, tuberculosis, Fiedler's myocarditis, and Chagas' disease. Rheumatic heart disease, Boeck's sarcoid, and echinococcus cysts are subacute to chronic in their effects. Vascular lesions such as coronary arteriosclerosis with anoxia, myocardial infarction, or diffuse fibrosis; angiitis due to rheumatic fever or periarteritis nodosa; and purpuras may cause damage by interference with the blood supply to the conduction system. Hypertensive disease causes physiologic changes by elongation and stretching of the pathways. Drugs such as the sulfonamides may produce an actual myocarditis. Neoplasms may be responsible for disturbances in conduction, particularly the metastatic type of which bronchogenic carcinoma and the lymphoblastomas are the most common; in rare instances, a primary tumor may cause arrhythmias. Various reflexes through the vagus nerves without demonstrable pathologic lesions, as seen with esophageal hiatal hernia and gall bladder disease, cause various arrhythmias and changes in conduction. At autopsy no gross or microscopic lesion has been encountered in many instances.

The signs and symptoms, as one may readily perceive, vary with the location of the lesion and to some extent with the type.

Yater and Cornell¹⁸⁰ reported 10 instances of complete heart block from the literature and added a case of their own. The defect in the main bundle in all of these cases was due to calcareous deposits located usually near the attachment of the aortic leaflet of the mitral valve. The bundle was interrupted as a rule near the junction of membranous and muscular portions of the interventricular septum.

ABNORMALITIES IN THE SIZE OF THE HEART

Hypoplasia.—Hypoplasia refers to underdevelopment of the heart. The heart is small in all dimensions and may weigh in the adult 200 grams or less. Hypoplasia of the aorta and arterial system usually accompanies the condition in the heart. In so-called status lymphaticus and in chlorosis the circulatory system may be hypoplastic.¹⁸¹

disease is enlargement of the heart.¹⁸³ Cardiac hypertrophy is a relative state since the increase in bulk of the myocardium must be compared with body weight. Increased bulk is the result of increase in size of the individual muscle fibers. The comparison of a normal heart (300 grams) with an enlarged heart (500 grams) and an atrophic heart (165 grams) resulted in a ratio of fiber size of the order 5 : 9 : 4, respectively.¹⁸²

Two kinds of cardiac hypertrophy are recognized, *concentric* and *excentric*. In the former the myocardium is thickened while the chambers appear to be smaller than usual. In the excentric type the chambers are dilated in addition to in-

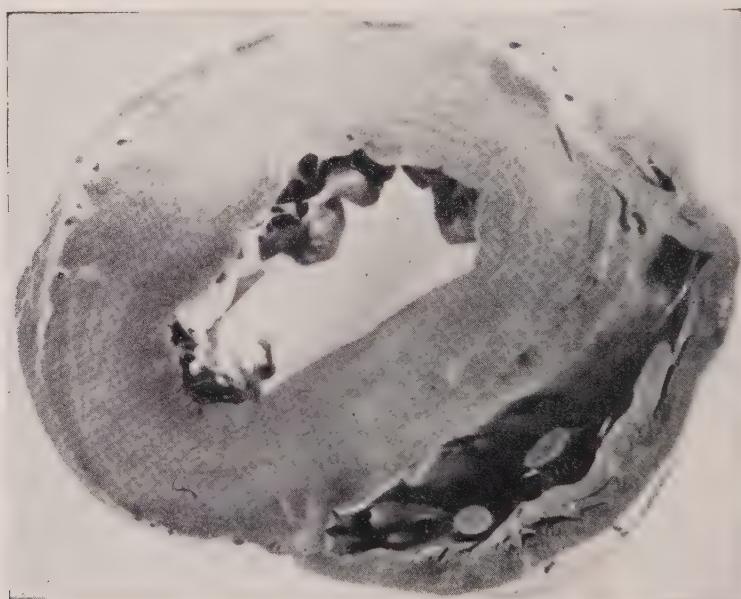


Fig. 378.—Hypertrophy of left ventricle in chronic hypertension. Note excessively thickened wall of left ventricle as compared with wall of right ventricle. The heart has been cut transversely through the ventricles. (From Anderson, Synopsis of Pathology, The C. V. Mosby Co.)

Atrophy.—The term *atrophy* is used to indicate reduction in size of a heart that had previously reached full development. The reduced size is due principally to shrinkage of the individual fibers; however, some fibers disappear altogether since the number of fibers in the entire heart is definitely decreased. In proportion to the number of fibers the number of nuclei is greatly increased.¹⁸² The atrophic muscle may be of normal color in young persons but it is usually distinctly brown in older people. *Brown atrophy* of the heart is discussed on pages 87 and 471.

Hypertrophy and Dilatation.—The cardinal objective sign of organic cardiac

increased thickness of the wall. A left ventricular wall 15 mm. in thickness represents considerable hypertrophy provided the chamber is well dilated. In concentric hypertrophy the wall may average 18 to 20 mm. in thickness (normal 10 to 12 mm.). (Fig. 378.) The muscle is firm, giving the impression of great power and abundant reserve. The papillary muscles and columnae carneae are rounded and sturdy. Microscopically the muscle fibers are uniformly thickened. According to Starling's³ law of the heart,

hypertrophy is preceded by dilatation of the chambers due to stretching of the individual muscle fibers. Presumably this is the result of overfilling the heart in diastole. Only by increasing the surfaces for chemical reactions can increased mechanical energy be produced. In very large hearts weighing 600 to 800 grams (*cor bovinum*), dilatation of the chambers is always a prominent part of the increased size (Fig. 379).

The degree and location of the hypertrophy and dilatation are related to the character of the abnormal burden. A burden, to be effective in producing hypertrophy must be relatively continuous. Thus, athletes seldom have hypertrophied hearts, while patients with valvular disease or severe hypertension usually do. In hypertension and in aortic stenosis there may be marked hypertrophy of the left ventricle with little or none on the right. On the other hand, in certain pulmonary diseases, in uncomplicated mitral stenosis, in pulmonic stenosis, and in congenital septal defects, the right heart exhibits the greater change. Of course, when failure is marked, no portion of the heart will be without its share of excess burden and hence all parts may enlarge.

It is axiomatic that large hearts tend to fail. This is believed to be due to inadequate coronary blood supply. A capillary for each muscle fiber is true of both normal and hypertrophied hearts. As the fiber size increases, the vascular supply becomes less adequate and the muscle is in a state of relative anoxia, since the surface of the fiber through which the nutritive processes take place has increased only as the first power of the radius while the mass has increased as the square of the radius.¹⁸³

It is recognized that certain disturbances in the heart and circulation are likely to result in cardiac hypertrophy. Important among these are mechanical obstructive lesions in the heart or the great vessels due chiefly to valvular lesions (aortic regurgitation, aortic stenosis). Another factor is increased peripheral resistance which affects the systemic circulation. Examples are hypertension, arteriolar sclerosis, glomerulonephritis, chronic pyelonephritis, and tumors of the adrenal medulla. Certain congenital cardiovascular lesions may be effective, such as co-

arctation of the aorta, defects in auricular or ventricular septa, and so-called idiopathic lesions. Alterations in the myocardium may stimulate myocardial

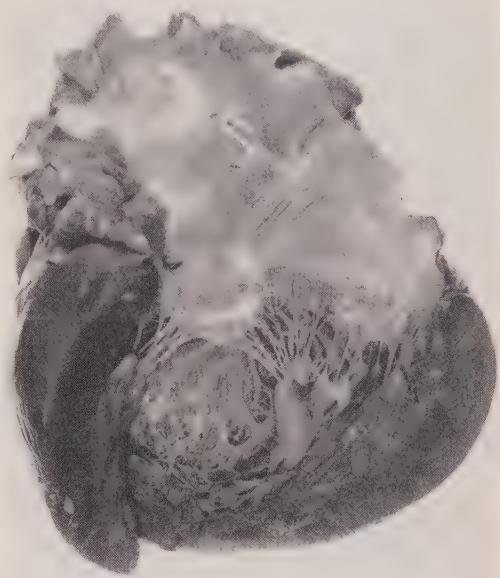


Fig. 379.—Hypertrophy of heart due to malignant hypertension. White male, aged 42 years. Blood pressure 280/170. Heart weighed 850 grams.

hypertrophy (old infarcts, arteriosclerosis with scarring, inflammations, and degenerations). *Cor pulmonale* may result from changes in the pulmonary circulation causing hypertrophy of the right ventricle, such as chronic passive congestion, pulmonary fibrosis and arteriolar sclerosis, emphysema, and bronchiectasis.¹⁸⁴ It is a condition produced by obstruction to the pulmonary blood flow resulting in hypertrophy of the right ventricle and finally the right auricle. Fibrosis and emphysema obliterate many of the pulmonary capillaries. Arteriolar sclerosis of the pulmonary vessels occurs typically in a syndrome known as Ayerza's disease. The patients often designated "black cardiae" have intense cyanosis, pulmonary fibrosis, and polycythemia.

Pathogenesis of Arterial Hypertension.—Hypertension may be defined as elevation of blood pressure over 150 systolic and 90 diastolic. It is not a disease

entity but a manifestation of a number of disease processes. In the vast majority of cases (90 to 95 per cent), however, the pathogenesis is obscure. This group constitutes the clinical entity of idiopathic, or essential hypertension.

The principal causes of hypertension (modified from the classification by Page and Corcoran¹⁸⁵) are:

1. Conditions affecting the renal vessels (arteriolosclerosis, polyarteritis, arteritis, mechanical obstruction due to thrombi, tumors, Buerger's disease, etc.).

2. Conditions affecting the renal parenchyma (nephritis, pyelonephritis, polycystic disease, amyloidosis, infarction, toxemia of pregnancy, etc.).

3. Conditions affecting the perinephritic structures (perinephritis, tumors, hematoma, etc.).

4. Obstructive uropathies (enlarged prostate, stones, tumors).

5. Cerebral factors (increased intracranial pressure due to trauma, tumors, inflammation, diencephalic stimulation, anxiety states, lesions of the brain stem).

6. Cardiovascular lesions (heart failure, arteriovenous fistula, angina pectoris, heart block, coarctation of aorta, etc.).

7. Endocrine changes (pheochromocytoma, adrenal cortical tumors, chorionepithelioma, pituitary adenoma (basophilic and eosinophilic), hyperthyroidism, arrhenoblastoma).

8. Unknown (essential hypertension).

Possible immediate mechanisms in the production of hypertension include increase of cardiac output, blood volume, blood viscosity, and peripheral vascular resistance. Recent investigations have pointed to widespread increase in arteriolar tone as the principal mechanism in essential hypertension.¹⁸⁶

Both neurogenic and humoral factors have been stressed as possible causes for increased arteriolar tone. Studies of humoral mechanisms have centered about the kidney, the relation of which to hypertension was first suggested by Richard Bright.¹⁸⁷ It is noteworthy that of the known causes of hypertension more than half are of renal origin and that in man hypertension has been reduced by removal of a single damaged kidney. In an admirable series of experiments, Goldblatt^{188, 189} has shown that hypertension can be produced by renal ischemia. Page and Helmer¹⁹⁰ and Houssay¹⁹¹ showed that ischemic kidneys contain a substance, renin, which acts on the blood plasma to produce a pressor agent.

Although the association between hypertension and arteriolar sclerosis of the kidney is undoubtedly, it is difficult to decide which is cause and which is effect. Moritz and Oldt¹⁹² have shown the very high degree of correlation between the two and the lack of correlation between hypertension and splenic arteriolosclerosis. Renal arteriolosclerosis should be an efficient

cause of renal ischemia comparable to that induced by the Goldblatt¹⁸⁸ clamp. And yet it is certain that hypertension may precede and induce arteriolar changes, and the studies of Castleman and Smithwick¹⁹³ suggest that marked renal arteriolosclerosis is a late rather than an early finding in essential hypertension (see also page 566).

Although Goldblatt¹⁸⁹ found that total sympathectomy did not modify the hypertension in his experimental animals, whether done before or after the alteration of renal blood flow, in man some hypertensive patients respond to sympathectomy as shown by lowering of blood pressure and improvement of symptoms. It would seem that the neurogenic element is probably effective as the basis of the early phases of hypertension, as suggested by Page.¹⁸⁵ Spasm of the renal arterioles, together with increased vascular pressures operative over a period of months or years, initiates degenerative changes in the renal vessels. As renal ischemia develops, the humoral mechanism comes more and more into play, gradually replacing the neurogenic element. By this time, chronic hypertension of the essential type is established. Under the stress and strain of fixed high blood pressure, degenerative vascular changes progress not only in the renal bed but in widespread areas throughout the vascular system. A vicious cycle is thus established which tends to ever increase the hypertensive state.

Effects of Hypertension.—Effects of hypertension may be manifested chiefly in the heart, the brain, or the kidneys. In 2,597 fatal cases reviewed by Clawson¹⁹⁴ death was attributed to myocardial insufficiency in 43 per cent, to coronary artery disease in 36 per cent, to cerebral hemorrhage in 14 per cent, and to renal insufficiency in 7 per cent.

Hypertensive Heart Disease.—Even when the major burden falls elsewhere, hypertensive patients almost invariably show some degree of cardiac pathologic change at autopsy, and the majority of hypertensive deaths are essentially cardiac. Hypertension of the systemic circulation is the basic cause of 55 per cent of all cardiac deaths.¹⁹⁴ There are two principal ways in which hypertension may injure the heart: (1) by the increased burden on the heart muscle, resulting in hypertrophy and eventual anoxia; (2) by the enhancement of coronary sclerosis. In many cases both factors are operative.

MISCELLANEOUS CARDIAC DISTURBANCES

The Heart in Deficiency Disease (Beriberi)

Occasional obscure types of cardiovascular dysfunction are seen in dietary deficiency, especially that due to insufficient vitamin B₁ (thiamine). The disease, *beriberi*, long known

among peoples of the Orient, is characterized in the "dry" form by muscle wasting and peripheral neuritis, in the "wet" form by cardiovascular disturbances and edema.¹⁹⁵

Pathologic Anatomy.—The heart is usually enlarged and is often described as globose. There is marked dilatation affecting mainly the right ventricle. The wall of the right ventricle may measure 5 to 7 mm. in thickness, while the left ventricle measures only 3 to 5 mm.¹⁹⁶ Adult hearts frequently weigh 500 to 600 grams. The average weight of the heart in five cases reported by Dock was 629 grams. (Fig. 380.) Microscopically there is edema of the interstitial tissue. On cross section the subendocardial muscle fibers, especially, may exhibit vacuoles in the center of the fibers due to hydropic degeneration. Fatty degeneration has been reported in some instances. All of Dock's¹⁹⁶ patients presented mural thrombi among the trabeculae carneae of the ventricles.

The Heart in Myxedema.—Hypothyroidism in adults occasionally results in a condition known as myxedema. Many authors have reported cardiac enlargements in myxedema,¹⁹⁸ while others¹⁹⁹ have found only occasional cardiac involvement. The sex ratio is 4 females to 1 male. The disease appears usually in middle life. There is a striking analogy between the occurrence of arteriosclerosis in diabetes and in spontaneous myxedema. Sclerosis of arteries begins early in the disease regardless of the patient's age. It is interesting that the cholesterol blood level is high in both conditions.¹⁹⁸ The enlarged heart tends to be globular in form, due mainly to dilatation. Microscopically, the sarcoplasm of the myofibrils is often replaced by hydropic vacuoles. There are loss of striations and variation in nuclear staining, some nuclei being pale, others pyknotic. The close similarity to the micro-



Fig. 380.—Heart in beriberi. Note globular form with hypertrophy and dilation of left ventricle. Chronic alcoholic, aged 46 years.

The Heart in Thyroid Disease

In hyperthyroidism the heart undergoes hypertrophy and dilatation due to the increased work caused by the higher metabolism. There is increased minute volume output with a correspondingly greater venous return. A small group of these patients develop auricular fibrillation and, later, congestive cardiac failure. Often there is an underlying cardiac lesion which predisposes to failure.¹⁹⁷ The heart is often moderately enlarged due to hypertrophy and dilatation. Hydropic degeneration may be present in the muscle fibers similar to that seen in beriberi heart. Hyaline necrosis may appear in scattered fibers and loss of cross striations is fairly common. (See also page 1001.)

scopic picture in beriberi heart make it evident that the changes are not specific. (See also page 1003.)

The Heart in Acromegaly

The extreme cardiac hypertrophy observed in this disease is no doubt part of the general visceral hypertrophy (splanchnomegaly) which regularly occurs in this condition. The changes are believed to be due to the effect of the growth hormone emanating from the eosinophilic cells of the pituitary adenoma which is the specific lesion in this disease.^{200, 201}

Grossly, the huge heart tends to present an elongated axis which is perhaps indirect evidence that the hypertrophy is due to a growth stimulus. Histologically, hypertrophy of muscle



Fig. 381.—Myxoma of the heart. Note the smooth glistening tumor attached to the septal wall of left auricle and partly blocking the mitral orifice.

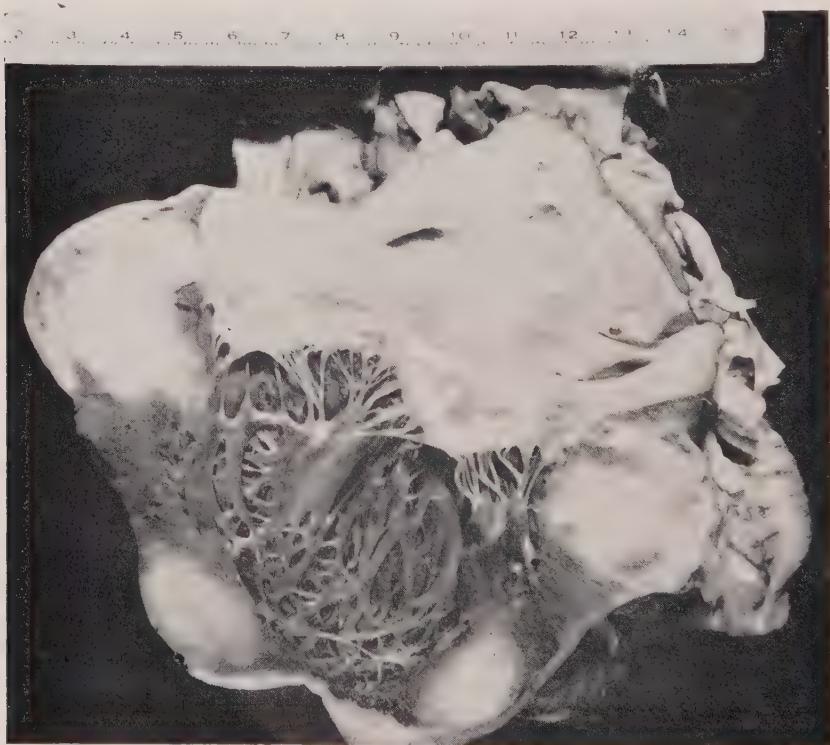


Fig. 382.—Metastatic tumor in myocardium from a hypernephroma.

fibers is present and the supporting connective tissue is markedly and diffusely increased. Scarring of the muscle may be present.

The Heart in Anemia

Fatty degeneration of the myocardium is common in severe anemias. In high-grade anemias, as in hyperthyroidism, there is increased minute output of blood, increased pulse pressure, and increased oxygen consumption.²⁰² The heart frequently undergoes work hypertrophy,²⁰³ murmurs develop which may be indistinguishable from those caused by valvular disease, and angina pectoris may be present in the absence of coronary artery disease or myocarditis.^{204, 205} These symptoms may disappear and the heart may return to normal size if the anemia is cured.²⁰⁴

Tumors of the Heart

Primary tumors of the heart are rare. One hundred and sixty-three primary tumors had been reported up to 1945.²⁰⁶ Tumors reported include myxomas, fibromas, lipomas, endotheliomas, leiomyomas, rhabdomyomas, and their corresponding sarcomas. Approximately 20 per cent have been malignant. Males are affected twice as often as females, the tumors usually occurring in the younger age groups.²⁰⁷ The myxoma has been reported most frequently. Husten²⁰⁸ has expressed the belief that many of these tumors are organized thrombi. Although primary tumors may occur anywhere in the heart, by far the greater number are found in the left auricle. The myxoma is usually rounded or cylindrical in form, with smooth, glistening surface. It is often mottled, varying from pale yellow or gray to reddish-brown in color. In the left auricle it is attached to the posterior wall of the interauricular septum. (Fig. 381.) Microscopically, the stroma consists of pale mucoid material with scattered star-shaped connective tissue cells. The degree of cellularity varies often in different areas. The fibromas are more cellular, with fusiform cells predominating.

Secondary tumors of the heart are also quite rare but occur more frequently than do the primary tumors. They may come from a primary tumor in any organ. More commonly, however, they are derived from hypernephromas and other tumors which tend to grow into the vena cava and from the widely disseminated lymphoblastomas and melanomas (Fig. 382).

CONGENITAL HEART DISEASE

Congenital heart disease is that condition in which abnormalities in the anatomical relationships of the heart or great vessels occur as the result of disturbances in development. These changes may be only minor, causing no serious symptoms or signs, but nevertheless introducing the factor of cardiovascular strain which after a period of years terminates in

congestive failure. Even when relatively inconspicuous, congenital cardiac lesions may provide a *locus minoris resistentiae* favoring the development of subacute bacterial endocarditis. Or otherwise, they may be of such a nature as to produce profound changes in the circulation preventing proper oxygenation of the blood, resulting in extreme cyanosis, clubbing of fingers and toes, and often terminating life at an early age. The more extreme lesions are incompatible with life, death intervening within a few hours or days after birth. In the more severe cases there is usually a permanent shunt of venous blood into the greater circulation.

It is generally agreed that the great preponderance of cardiac anomalies have their inception during the fifth to eighth weeks of embryonic life. It is during this critical period that the tubular heart undergoes torsion and kinking with formation of sacculations which later become divided into separate chambers by the ingrowth of septa. Finally, these contortions of the developing heart result in a four-chambered organ with complete separation of venous and arterial blood. Any interference with normal growth processes during this early period necessarily produces changes that result in serious deformities in the course of further development.

Etiology.—The basic etiology of most cardiac anomalies is unknown. The mechanism of production is probably related to arrests of growth plus the dynamic action of the blood stream as it courses through the developing organ. In general the etiological factors are either intrinsic or extrinsic in origin.²⁰⁹

Intrinsic Factors.—Intrinsic factors are those due to faulty germ plasm or hereditary tendencies. Defects in the genes are surmised by the knowledge that multiple congenital malformations have been reported in members of the same family.²¹⁰ The 1,000 cases of congenital heart disease collected by Abbott^{211, 212} presented in 188 or 18.8 per cent, congenital lesions in other organs or parts.

Extrinsic Factors.—Severe vitamin deficiencies in the mother during pregnancy are suspected of playing a role. Skeletal deformities especially of the spine may modify the rich vascular bed of the embryo sufficiently to cause abnormalities in the development of the heart or great vessels. That virus infections play a role in producing abnormalities in the embryo seems to be proved by the reports of Gregg,²¹³ Swan,²¹⁴ and others. German measles in the mother during the first two months of pregnancy is associated with a high incidence of congenital cataracts and congenital cardiac defects. Taussig²⁰⁹ states that in her experience syphilis and fetal endocarditis are relatively unimportant or actually nonexistent factors in the production of congenital anomalies of the heart. Recently, Butt and Simonsen²¹⁵ have demon-

strated relatively large amounts of heavy metals, especially lead, in the tissues of infants who have died due to congenital disease.

Incidence.—Autopsy statistics reveal an incidence of congenital heart disease of about 8 per 1,000 if stillbirths are included.²¹⁶ About 10 to 15 per cent of all cardiac lesions are congenital. In a clinical study of nearly 120,000 Boston school children, 625 organic cardiac lesions were found, of which 69, or 11 per cent, were congenital.²¹⁷

Associated Diseases.—Bacterial endocarditis is the most serious condition associated with or engrafted on a congenital cardiac lesion. It is most often seen in cases of bicuspid aortic valve, patent ductus arteriosus, and open interventricular septum. A high percentage of patients with pulmonary stenosis develop pulmonary tuberculosis, amounting in Abbott's²¹¹ cases to 36 per cent. Mongolian idiocy is associated with congenital heart disease in about the ratio of 1 to 10.

The aorta may rupture spontaneously in coarctation of the aorta, caused by the dilatation and greatly increased pressure in the ascending aorta. A tear may develop at the seat of constriction due probably to traction on the obliterated ductus. Paradoxical embolism, a condition in which an embolus formed on the venous side comes to lodge in the arterial system, occurs rarely. In such instances there must be present a patent foramen ovale or interventricular septal defect.

Anatomical Classification

(Modified from Abbott²¹¹)

1. *Anomalies of the Heart as a Whole*
 - Ectopia Cordis
 - Dextrocardia
 - Congenital Idiopathic Hypertrophy
 - Endocardial Sclerosis
 - Congenital Rhabdomyoma
2. *Defects of Interauricular and Interventricular Septa*
 - Patent Foramen Ovale
 - Defects of Interauricular Septum
 - Persistent Ostium Atrioventriculare Communis
 - Localized Defects of Interventricular Septum (Maladie de Roger)
 - Congenital Aneurysms of Interventricular Septum
3. *Truncus Arteriosus or Anomalous Development of the Great Vessels*
4. *Transposition of the Arterial Trunks*
5. *Pulmonary Stenosis and Atresia*
 - Tetralogy of Fallot
 - Eisenmenger's Complex
6. *Aortic and Mitral Atresia With Rudimentary Left Ventricle*
 - Tricuspid Atresia With Rudimentary Right Ventricle
7. *Anomalies of Chordae and Endocardium*
 - Chiari's Network
 - Fenestration of Semilunar Valves
 - Subaortic Stenosis
 - Bicuspid Aortic Valve
8. *Patent Ductus Arteriosus*
9. *Coarctation of the Aorta*
10. *Anomalies of the Coronary Arteries*

ANOMALIES OF THE HEART AS A WHOLE

Ectopia Cordis.—This is a rare anomaly in which the heart is outside the body cavity and usually attached over the anterior middle part of the chest. Abbott²¹¹ reported 8 cases among the 1,000 congenital hearts studied.

Dextrocardia.—In this condition the heart is on the right side of the chest with the apex pointing toward the right side. Dextrocardia may be *congenital* or *acquired*. The acquired form is usually referred to as *dextroposition cordis*. *Dextrocardia with complete situs inversus* of the viscera (mirror image) is not properly a form of congenital cardiac disease, and, while an interesting phenomenon, it is of no clinical significance. The incidence postmortem is about 1 in 5,000.²¹⁸ *Dextrocardia with partial situs inversus* is a rare condition associated in most instances with complex cardiac malformations. *Isolated congenital dextrocardia*, also rare, refers to a right-sided heart with normal position of all other viscera. Grave cardiac anomalies are always present. The acquired form, *dextroposition cordis*, is due usually to postnatal pathologic processes such as inflammations with resulting adhesions or fibrous bands, trauma, tumors, etc., which lead to decrease in volume of the right or to increase in volume of the left thoracic space. The mediastinum is displaced to the right as indicated by the cardiac axis.²¹⁹

Congenital "Idiopathic" Hypertrophy.—Idiopathic cardiac enlargement or congenital idiopathic hypertrophy consists of enlarged heart without valvular disease or other congenital defects occurring in infants aged about 3 months to slightly over a year. The clinical picture is that of heart failure in an infant with an enlarged heart. Two types should be differentiated: (1) hypertrophy without obvious cause; (2) hypertrophy due to myocardial or other related disease. In recent years, the latter group has greatly increased while the former group has become noticeably smaller. Many hearts formerly classified in the first group have been found to contain glycogen in considerable quantities (von Gierke's disease). Other cases on microscopic examination show subacute or chronic myocarditis with lymphocytic infiltration of the myocardium.^{220, 221}

Congenital Rhabdomyoma.—Congenital rhabdomyoma is a rare condition characterized by the development of single or multiple tumor-like nodules in the myocardium, usually associated with tuberous sclerosis of the brain and somewhat less frequently with renal cysts and tumors. The nodules in the heart are believed to be tissue malformations and not true tumors.^{222, 223} Up to 1951, only 70 cases of congenital rhabdomyoma had been recorded.

Endocardial Sclerosis.—The rare condition of endocardial sclerosis is characterized by cardiac enlargement in infancy followed by congestive failure. The heart is three to five times normal weight, usually globular in form, with marked dilatation of the left ventricle. The chief lesion is that of thickening and fibrosis of the endocardium of the left ventricle and less frequently of the right ventricle. The endocardium has a white, thick, opaque appearance involving the entire lining of the ventricle

and at times involving a portion of the left auricular endocardium. The theory that endocardial sclerosis is due to a developmental defect with resultant hyperplasia of the endocardial tissues has much in its favor.²²⁴

These infants die of cardiac failure which is probably due to two factors: (a) scarring of the endocardium (infarcts?) due to obliteration of the arterioluminal, arteriosinusoidal, and thebesian vessels (Gross²²⁵), and (b) increased strain put upon the heart by the stiffness of the endocardial layer.

patients then develop cyanosis (cyanose tardive) and clubbing of the digits. The pathologic changes consist of a small aorta and left ventricle, dilatation of the pulmonary artery, dilation and hypertrophy of the right auricle and ventricle. There is usually severe chronic passive congestion of the lungs, liver, and viscera. For a discussion of etiology and for the various anatomical types of patent foramen, consult Patten's²²⁷ excellent paper.

COMPLICATIONS.—In patent foramen ovale paradoxical embolism may occur. Only about 30



Fig. 383.—Endocardial sclerosis. Negro female infant of 7 months. Heart weight 77 grams. About three times normal for the age.

DEFECTS OF INTERAURICULAR AND INTERVENTRICULAR SEPTA

Patent Foramen Ovale.—The foramen ovale ordinarily closes, at least functionally during the first few minutes after birth. Anatomical obliteration requires a much longer period than is usually stated. Scammon and Norris²²⁶ claim that only about 50 per cent become anatomically obliterated by the end of the first year. For many years the foramen may be probe-patent but functionally closed since the valve flap is on the left side of the septum where the pressure is higher than on the right.

When the foramen ovale remains patent, blood passes through the opening from left to right because of the higher pressure on the left. The blood pressure is higher in the left auricle as compared with the right probably because of greater tonus in the musculature of the left side. In childhood the shunt is seldom of sufficient volume to produce cyanosis.²⁰⁹ In time, usually after many years, pathologic changes may occur in the lungs which cause the pulmonary pressure to rise. Terminally, a reversal of flow may take place in which blood passes through the defect from right to left. These

cases have been reported; in seven of these a thrombus was found straddling the foramen.²²⁸ Pulmonary embolism is often encountered in patent foramen ovale.

Auricular Septal Defects.—Auricular septal defects are usually of relatively large size, measuring 2 to 3 cm. in diameter. The location of these is variable. If the defect is near the lower border of the septum, it is probably a *persistent ostium primum*. The auricular septal defect differs from a patent foramen ovale in that the opening is not covered by a valve or membrane, thus a free communication exists between the two auricles. As long as the interauricular pressures are nearly equal on the two sides, no significant changes occur.

Mitral stenosis is commonly associated with auricular defects. It is often difficult to judge whether this is congenital or rheumatic in origin. In this condition, the blood pressure tends to be high in the left auricle causing a left-to-right shunt with strain on the right side of the heart. In time, the right auricle, right ventricle, and pulmonary artery become dilated and the right cardiac chambers hypertrophied. The left ventricle and aorta are relatively small. This combination of auricular septal defect, combined

with congenital or acquired mitral stenosis and huge dilatation of the pulmonary artery, is called *Lutembacher's syndrome*.²⁰⁹

Clinical Features in Lutembacher's Syndrome.—The patient has a frail build and is poorly developed. There is no deep cyanosis and no clubbing since the shunt is from left to right. The contour of the heart is characteristic in the x-ray. It is often of huge size especially the right auricle and right ventricle, with prominent pulmonary conus and increased hilar shadows.

Pneumonia, pulmonary infections, and pulmonary emboli are frequent complications in auricular septal defects while bacterial endocarditis is exceedingly rare.²⁰⁹ Complete absence of the interauricular septum may occur without changes in the ventricles (*cor triloculare*

circulation is adequate, there is usually no cyanosis but the degree of oxygen saturation of the blood is definitely low.²⁰⁹

Persistent Ostium Atrioventricularare Commune.—In this condition a defect in the lower part of the interauricular septum (persistent ostium primum) is combined with a defect in the upper part of the interventricular septum. When the defect is large, the heart is essentially a biloculate organ with a common atrioventricular opening guarded by a continuous valve with five leaflets.²¹¹

Transposition of the great trunks or persistent truncus arteriosus may complicate defects of the auricular septum. These constitute severe forms of *morbus caeruleus* with death occurring most commonly in infancy.

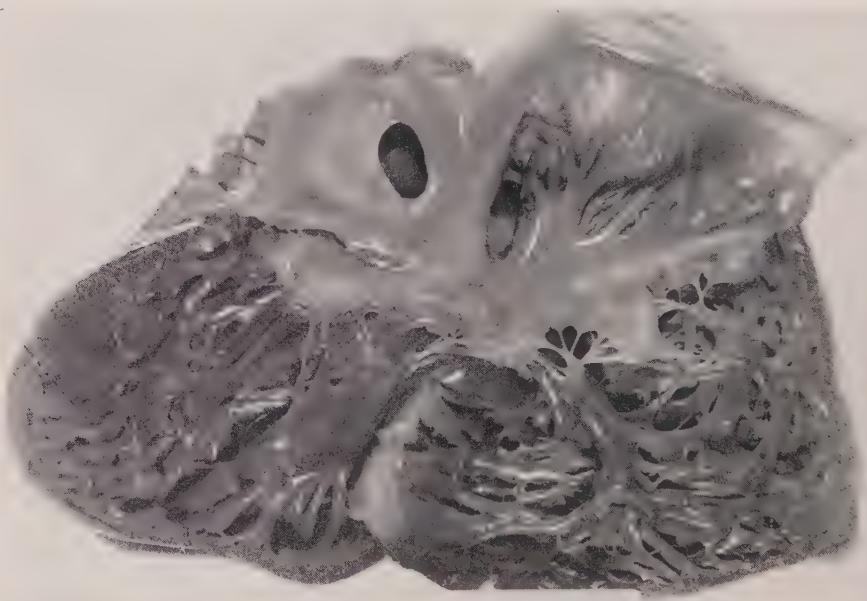


Fig. 384.—Patent foramen ovale with marked hypertrophy and dilatation of the right ventricle. Negro woman, aged 41 years. Patient always dyspneic; increasing orthopnea for the past three years. Death due to right heart failure.

biventriculare). If uncomplicated, this condition produces much the same clinical course as in local defects of the auricular septum. When other anomalies are present such as transposition of the great trunks, pulmonary arteria, and congenital dextrocardia, life is likely to be measured in weeks or months. Mongolian idiocy may be associated, as it often is, in local defects of the auricular septum.²¹¹ A complete defect of the interventricular septum may exist with a sound interauricular septum (*cor triatriatum triloculare*). Blood from both auricles is mixed in the common ventricle and passes into systemic and pulmonary circulations via aorta and pulmonary artery respectively. The patient may reach middle age in uncomplicated cases.

Cyanosis and clubbing are present if the pulmonary artery is small or relatively small as compared with the aorta. If the pulmonary

Localized Defects of Interventricular Septum (Maladie de Roger).—The usual site of localized interventricular defects is at the base of the septum anterior to the *pars membranacea*. Since the blood flow through such defects is from left to right, they are said to open into the right ventricle. These cases are excellent examples of an arteriovenous shunt of developmental origin. The openings are often small and the volume of shunted blood is not sufficient to cause strain on the right heart. Consequently there may be little change in the two ventricles as to volume and thickness of wall. Cardiac efficiency is not curtailed and therefore no symptoms are produced. Physical signs, however, are usually characteristic. A long-drawn-out harsh murmur is heard best over the fourth left interspace often accompanied by a thrill. The smaller openings (3 to 4 mm. in diameter) pro-

duce the loudest murmurs. The combination of asymptomatic cardiac disease with distinctive physical signs was first described by Rogers²²⁹ in 1879. It is now generally referred to as *maladie de Roger*. Bacterial endocarditis may be engrafted on the edges of the septal defect. The more serious congenital complications of interventricular septal defects such as transposition of the great trunks and atresia of the pulmonary artery are considered later. Defects of the interventricular septum are among the most common congenital anomalies. There were 207 cases in Abbott's^{211, 212} series, 50 of which were uncomplicated, the remainder in association with other malformations.

TRUNCUS ARTERIOSUS OR ANOMALOUS DEVELOPMENT OF THE GREAT VESSELS

In truncus arteriosus there is an early arrest in the development of the great vessels. A single large trunk leaves the base of the heart and carries blood to the lungs and to the systemic circulation. There are two types: (a) the pulmonary artery may fail to connect with the aorta so that the lungs are supplied with blood by way of the bronchial arteries, or (b) the pulmonary arteries arise directly from the common trunk. Since the single trunk overrides the ventricular septum it carries blood from both ventricles. This necessitates a high interven-

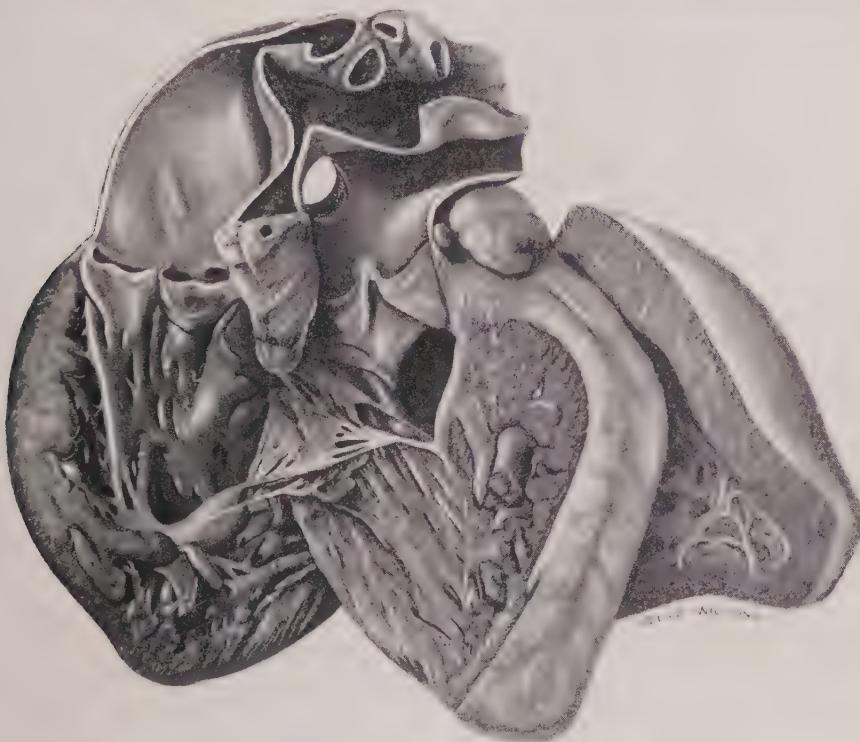


Fig. 385.—Transposition of great arterial trunks and of the cardiac chambers (drawing). Note the aorta arising from the right side of the heart identified by coronary ostia (only one is in view) and by the arteries coming off the arch. The pulmonary trunk rides over the defect in the interventricular septum. The mitral valve is on the right side, thus identifying this chamber as the "left ventricle." The ventricles are both greatly hypertrophied. The venous blood passes out through the aorta, and the oxygenated blood is largely sent back to the lungs. The intermixiture through the large septal defect made life possible, at least for a few years. Boy, aged 7 years. Extreme cyanosis, marked clubbing of fingers and toes. Death due to cerebral hemorrhage.

Congenital Aneurysms of Interventricular Septum.—These are usually small defects seen on the left side of the heart involving the region of the membranous septum. The openings, which are only a few millimeters in diameter, expand into thin-walled sacs which project into the right ventricle near the median leaflet of the tricuspid valve or rarely into the right atrium.^{230, 231}

tricular septal defect which is a definite part of the malformation. The ventricles are hypertrophied since they pump blood into both circulations. The right ventricle becomes greatly enlarged.

If the circulation to the lungs is by way of the bronchial arteries, the amount of aerated blood is small and cyanosis is usually intense, accompanied by clubbing and polycythemia.

If the pulmonary arteries arise from the common trunk as in (b) a large amount of blood reaches the lungs for aeration and cyanosis is not present. Patients with cyanosis in which the pulmonary arteries are absent live only a few days or weeks. Those with adequate circulation to the lungs may live for several years. The Blalock-Taussig operation may improve the prognosis considerably.^{209, 232, 233}

TRANSPOSITION OF THE ARTERIAL TRUNKS

Transposition of the great arterial trunks refers to that condition in which the aorta and pulmonary artery are transposed in relation to

Spitzer,^{234, 235} in his study of the hearts of the lower animals, found in the reptilian heart the key to transposition of the great vessels in man. He postulated that the formation of septa in the heart is intimately correlated with the appearance and development of the lungs through phylogeny. The development of lungs for air breathing made it necessary for the two circulations to be separated. The clockwise torsion of 180 degrees, through which the bulbar end of the heart passes, results in the great vessels which arise by longitudinal division of the bulbous cordis coming to lie in a crossed or intertwined position—the aorta lies slightly anteriorly and to the left coming off

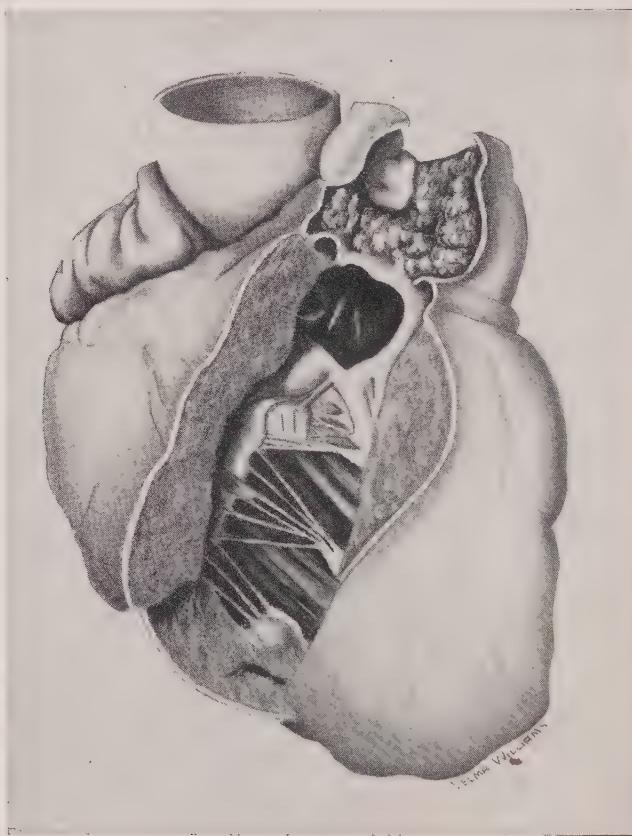


Fig. 386.—Tetralogy of Fallot (drawing). Note the four anomalies: 1, pulmonic stenosis; 2, dextroposition of aorta; 3, large interventricular septal defect; 4, marked hypertrophy of right ventricle. The narrow pulmonic valve is the site of a vegetative endocarditis.

each other so that the vessels arise from ventricles opposite to the normal. This is in complete transposition. A number of variations occur in the positions of the arterial trunks relative to one another. These will be considered later. Complete transposition is a baffling condition which on first impression appears to be embryologically inexplicable. Alexander Spitzer, working in Vienna, presented a theory on the etiology of transposition which is generally accepted at the present time. This theory is based on *phylogeny* instead of *ontogeny*.

the left ventricle, while the pulmonary artery lies posteriorly and to the right communicating with the right ventricle. Spitzer based the actual mechanism of transposition on (a) failure of complete torsion or a "detorsion" in the development of the bulbar end of the cardiac tube. If the usual clockwise torsion of 180 degrees is arrested, there will be an apparent effect of shunting the parts in a counterclockwise manner and thus forcing them out of their normal relationships. The other important factor (b) is that of opening up the channel of the reptilian right

aorta and at the same time obliterating the left ventricular aortic trunk. (See paper by Harris and Farber²³⁵ for description in English.)

PULMONARY STENOSIS AND ATRESIA

The seriousness of the lesions in which pulmonary stenosis and atresia are present is largely dependent on the condition of the fetal passages. A defect in the interventricular septum in *pulmonary stenosis* increases the gravity of the condition by adding a venous-arterial shunt which augments the effects of obstruction in the pulmonary circulation. In *pulmonary atresia*, however, the presence of a defect eases the strain on the right ventricle by providing an opening by which the obstructed venous blood may enter the left ventricle and thence reach the lungs by way of the aorta and a patent ductus arteriosus. Among the 150 cases of pulmonary stenosis and atresia in Abbott's series, the 16 with pulmonary stenosis and *closed ventricular septa* had the best prognosis. The mean age was 18 years. Among the pulmonary atresias the highest mean age for 12 cases was 6 years (closed foramen ovale with defect in interventricular septum).²¹¹ The foramen ovale is frequently patent. Cyanosis comes on late, often due to bacterial endocarditis developing in the already damaged valve, thus reducing the size of the stenosed opening. Clubbing is present and usually progressive.

Tetralogy of Fallot.—Fallot,²³⁶ in 1888, demonstrated that congenital heart disease associated with cyanosis, especially in adults, is usually the result of a complex of anomalies embracing pulmonary stenosis, interventricular septal defect, deviation in the origin of the aorta to the right, and hypertrophy of the right ventricle (tetralogy of Fallot) (Fig. 386). Patency of the foramen ovale is not essential although it may be present. Fallot collected 55 cases of severe cyanosis, in which 41, or 74 per cent, exhibited the tetralogy. The incidence of Abbott's²¹¹ series is practically the same, since 77 per cent of her cases of pulmonary stenosis and 66 per cent of the pulmonary atresias fall into this group. Thus, clinically, *morbus caeruleus* is usually the result of *tetralogy of Fallot* and should be so considered until proved otherwise. As a result of the raised pressure in the right ventricle due to pulmonary stenosis, a permanent venous-arterial shunt is produced through the defect in the septum. This condition is aggravated by the position of the aorta, which either rides over the defect thus receiving blood from both ventricles or it arises entirely from the right ventricle (Spitzer's Types I and II). The obstruction to the pulmonary outflow also creates a back pressure in the systemic capillaries resulting in increasing anoxia. A further effect of reduced pulmonary blood supply and increased pressure in the right ventricle is the development of collateral circulation to the lungs from bronchial and other mediastinal vessels. The circulation time may be a diagnostic aid in pulmonary stenosis or atresia with septal defect. The arm-to-tongue time is greatly shortened on account of the venous arterial shunt causing the greater volume of blood to bypass the lungs. The arm-to-tongue time is about 4 seconds under these

conditions. If the interventricular septum is closed, the time is normal (10 seconds) or prolonged.²³⁷ As these patients reach the terminal phase, they exhibit the picture of intense cyanosis and its secondary manifestations. The prognosis in tetralogy of Fallot as well as in some other of the cyanotic group of anomalies has brightened considerably in recent years because of improved surgical technique in restoration of a more nearly normal circulation. The Blalock-Taussig²³⁸ operation in which an anastomosis is made between one of the branches of the aorta (innominate or subclavian arteries) and one of the pulmonary arteries, creates an artificial ductus arteriosus which greatly increases the pulmonary circulation, increases the oxygen saturation of the blood, and reduces cyanosis and polycythemia.

*Eisenmenger's complex*²³⁹ resembles the tetralogy of Fallot in having a dextraposed aorta partially overriding the septum and, consequently, a high ventricular septal defect. It differs from the tetralogy in having a *dilated pulmonary artery* instead of pulmonary stenosis. Since there is no obstruction in the pulmonary outflow the right ventricle is usually not hypertrophied. Clubbing and cyanosis may be absent in infancy but tend to develop during adolescence.

AORTIC AND MITRAL ATRESIA WITH RUDIMENTARY LEFT VENTRICLE

Aortic and mitral atresia constitute the gravest lesions of the cyanotic group. The absence of collateral circulation other than through a patent ductus probably accounts for the poor prognosis. In aortic atresia the life span is measured in hours or days. The average of 12 cases in Abbott's series²¹¹ was four days. A male infant examined at autopsy by the author had been delivered by cesarean section and had survived six days. Deepening cyanosis had developed twelve hours before death. As is frequently the case, there was not only severe aortic hypoplasia but mitral atresia as well with rudimentary left ventricle. The pulmonary artery, which was dilated, connected with the aortic arch by means of a wide ductus arteriosus. The foramen ovale was open but the ventricular septum was closed. Circulation to the myocardium was greatly reduced since little blood could reach the coronary ostia.

TRICUSPID ATRESIA WITH RUDIMENTARY RIGHT VENTRICLE

Tricuspid atresia with defective development of the right ventricle is a rare anomaly. Venous blood enters the right auricle, passes through a patent foramen ovale or an auricular septal defect into the left auricle, thence to the left ventricle and out through the aorta. Pulmonary atresia is necessarily associated with a nonfunctioning right ventricle. Blood reaches the lungs only by means of a patent ductus. There is deep cyanosis.

ANOMALIES OF CHORDAE AND ENDOCARDIUM

Chiari's network^{240, 241} consists of a reticulum of fine or coarse fibrous threads traversing the cavity of the right auricle. Its attachment extends from the interatrial septum to the region

of the orifices of the coronary sinus and inferior vena cava.²⁴² Usually the condition produces no symptoms or signs but appears as an incidental finding. Rarely, a thrombus may form in the network and later produce pulmonary embolism. A single fiber not constituting a true network may run from right auricle to right ventricle, across the ventricle only or auricle only. Rarely, the left side of the heart is involved.

Fenestration of semilunar valves had been studied by Foxe²⁴³ who found one or more fenestrations present in 82 per cent of 300 consecutive hearts examined. Small openings appear in the membranous cusps between the slightly thickened valve rim and the closing edge. These are regarded as acquired defects by Foxe, who found an increase in frequency up to the seventh decade. The author suggests that slight fusion of the commissures (2 to 3 mm.) materially increases the incidence probably due to unequal tension on the cusps.

Subaortic stenosis consists of a thin fibrous shelf or ridge which projects from the inner wall of the aortic conus about 6 mm. below the valves. This ridge completely encircles the lumen and so gives rise to symptoms and signs of aortic obstruction. The condition is rare. The liability of developing bacterial endocarditis is paramount.²⁴⁴

Bicuspid aortic valve may be of congenital origin or may be acquired. The *congenital form* is most frequently found in childhood.²⁰⁹ This differs greatly from the acquired form which occurs in adults. In the former the leaflets are fused but remain thin and pliable. The raphe is a smooth slightly elevated ridge of uniform thickness. Microscopically it contains elastic tissue and shows no evidence of inflammation.²⁴⁵ In the *acquired form* the raphe is higher, less regular, and may be calcified. Microscopically, the raphe consists of hyalinized fibrous tissue which, in its distal half, exhibits vascularity and round-cell infiltration. The acquired bicuspid valve is no doubt due to rheumatic fever. Bicuspid aortic valves are of clinical significance mainly because of the frequency of superimposed bacterial endocarditis. In a study of 31 cases of subacute bacterial endocarditis, bicuspid aortic valves were present in 8 cases.^{246, 247}

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is essential to the fetal circulation before the lungs are expanded. Christie²⁴⁸ found in postmortem subjects that, at 12 weeks of age, 95 per cent had a closed ductus, while at one year of age, in 98.8 per cent the ductus was obliterated. Closure comes about by a process of obliteration (endarteritis) which is not well understood. Patent ductus has recently assumed renewed interest due to successful surgical intervention.^{249, 250}

Pathologic Physiology.—Patency of the ductus after birth produces essentially an arteriovenous aneurysm. No cyanosis is present in uncomplicated cases since oxygenated blood from the aorta flows through the ductus into the pulmonary artery. From 40 to 75 per cent of the blood pumped out of the left ventricle into the aorta becomes short-circuited through the ductus into

the pulmonary artery.²⁵¹ This causes the left ventricle to pump from two to four times as much blood as the right ventricle in a given period of time, thus impairing the cardiac efficiency.

Uncomplicated patent ductus presents a continuous machinery-like murmur over the pulmonic area and roentgenographic evidence of an enlarged pulmonary conus. A study of the life expectancy in 76 patients over 3 years of age showed that 50 per cent had died up to 30 years, and by 40 years 71 per cent had died, all of heart failure.²⁵⁰ In another series of cases, subacute bacterial endocarditis accounted for nearly 42 per cent of the deaths, while congestive heart failure accounted for 28 per cent.²⁵²

ANOMALIES OF THE CORONARY ARTERIES

Variations in the distribution of the coronary arteries are common. The more typical variations are seen in the often aborted left circumflex branch, which is replaced by a long typically circumflex branch similar to that usually found on the right side, and as a corollary of this an aborted and simplified right coronary artery.²⁵³ Quite frequently the right or left coronary has two small ostia instead of one large one. This means that the first large coronary branch comes off the aorta directly instead of springing from the coronary artery immediately distal to its origin. Forty-three cases have been reported to 1950 showing absence of one coronary, usually the left.²⁵⁴ Either one or both coronary arteries may arise from the pulmonary artery. Although the condition is rare, about 20 cases have been described in the literature. These are cases in which the *left* coronary arises from the pulmonary artery. If the collateral circulation is good with free anastomoses between the right and left coronary arteries, no symptoms develop. On the contrary, if anastomoses are poor, the patient may have attacks of angina pectoris (Soloff's²⁵⁵ patient, a male infant of 4½ months). Rarely, the right coronary arises from the pulmonary artery. Rarely also, both coronaries arise in this way—a condition which is incompatible with life.

Signs of Circulatory Congestive Disturbance

Cyanosis.—Cyanosis is the sign par excellence of the more severe types of congenital cardiac anomalies. It is seen characteristically in the late stages of Abbott's²¹¹ Group II (cyanose tardive) and in Group III (morbus caeruleus). It is seen also in congestive heart failure, asphyxia, and in toxic states when the oxyhemoglobin is partly changed to methemoglobin. Cyanosis depends upon the absolute concentration of reduced hemoglobin in the blood rather than on the ratio of reduced to oxygenated hemoglobin.²⁵⁶ About 5 Gm. of reduced hemoglobin per 100 c.c. of capillary blood are necessary to cause cyanosis. It is the blood in the capillaries and to a lesser degree in the small arterioles and venules of the subpapillary plexus which produces cyanosis of the skin.

Polycythemia.—A type of cyanosis called by Osler "congestion" or "ruddiness" exists in

patients who have an excessive number of red blood cells. This may be seen in congenital heart disease (right to left shunt), in people who dwell at high altitudes, in the newborn, and in polycythemia vera (Vaquez-Osler disease). The red cells may number from 7 to 12 million. The skin presents a dark color even in the absence of anoxemia due to the increased number of red blood cells per cubic millimeter. The blood is dark red and viscid. Thrombosis is a frequent complication.

Capillary Loops of Nail Beds.—The form of dilated capillaries in the nail beds viewed under a lens or dissecting microscope constitutes a diagnostic aid in differentiating congenital heart disease and congestive cardiac failure. In congenital cardiac disease the capillaries assume an inverted U form like a shepherd's crook and are distinctly larger than they are in congestive heart failure. In the latter the descending limb of the U is quite tortuous.

Clubbing.—Low oxygen tension in the capillaries, if present over a considerable period, causes broadening and thickening of the distal phalanges of both fingers and toes, called clubbing or pulmonary osteoarthropathy. There is thickening of the soft parts, and new bone may be laid down by the periosteum (see also page 1223).

THE PERICARDIUM

Anatomical Relations

The pericardium is a serous membrane in the form of a closed sac into which the heart has been pushed as the fist may be pushed into a partly inflated balloon. The connective tissue of the wall is abundantly supplied with elastic fibers lined by an elastic basement membrane supporting a single layer of endothelium. Under conditions of inflammation and regeneration these cells may become cuboidal or cylindrical. The pericardium consists of two layers: (a) The visceral layer (epicardium) covers the surface of the heart and the roots of the great vessels (aorta and pulmonary artery) to which it is firmly attached. (b) The tough parietal pericardium surrounds the epicardium and the heart. A small quantity of clear yellow fluid separates the two layers.²⁵⁷ This outer layer is anchored firmly to the central tendon of the diaphragm and is attached loosely to the sternum anteriorly and to the mediastinal structures posteriorly.²⁵⁸

Congenital anomalies of the pericardium are extremely rare. The one most frequently reported is a defect or absence of part of the parietal pericardium. Southworth and Stevenson,²⁵⁹ 1938, found only 46 authentic cases including their own, exclusive of 7 cases in monsters. They found that the defect was almost invariably on the left side, and so complete in 76 per cent of the patients that the heart and left lung were in a common serous cavity. Three-fourths of the subjects were males. In about half of the instances of pericardial defect, unexplained cardiac enlargement developed. The main difficulty arising from such

a defect is the increased hazard from pulmonary infection, since in 27 per cent death was due to pleuropericarditis.

Diverticulum of the pericardium may be of congenital origin but is probably acquired in the majority of instances.²⁶⁰ The diverticula vary in size from 0.5 to 12 cm. Slightly more than half are present on the right. Diverticulum may be confused in the roentgenograph with aortic aneurysm or dermoid cyst of the mediastinum.

Tamponade or Cardiac Compression

Pericardial disease is largely manifest by interference with the activity of the heart due to cardiac tamponade or cardiac compression. In 1877 Cohnheim²⁶¹ injected oil into the pericardium of animals and observed that as the intrapericardial pressure rose there was increase in the general venous pressure, a fall in systemic arterial pressure, and a decrease in the cardiac output. He made the deduction that an impediment to the filling of the cardiac chambers is produced by effusions of fluid into the pericardial sac, providing a certain degree of tension of its walls is attained. Aneurysm and other mediastinal tumors may obstruct the return of blood to the heart and thus effect a similar result. More recently, constrictive pericarditis has been added to the list.

Hydropericardium.—The pericardial sac usually contains from 5 to 30 c.c. of clear straw-colored fluid that contains a trace of albumin, is alkaline in reaction and low in specific gravity, though it often contains traces of fibrin. The quantity of fluid may increase to 100 or, perhaps, 150 c.c. before it is called *hydropericardium*. After death the fluid may be stained red by absorption of hemoglobin; it may be deep red or brown from hemorrhage; or, if icterus is present, it is golden yellow. The quantity of fluid in the pericardium in hydrops varies from 200 or 300 c.c. up to 1 or 2 liters. The condition may be part of a general anasarca due to circulatory disturbances, subacute glomerulonephritis, chronic nephrosis, or myxedema. It is frequently an agonal phenomenon in congestive cardiac failure.

Since pleural fluid may also collect in the above conditions, the combined effect results in varying degrees of dyspnea. In such instances, the vital capacity of the lungs is reduced because of hydrothorax, and at the same time the

venae cavae are compressed by the excess pericardial fluid, thus slowing return of venous blood to heart and lungs. The element of time is important, as 300 to 400 c.c. of fluid accumulating quickly in the pericardial space may produce more disturbance than a liter of fluid which has collected slowly. Large quantities of pericardial fluid (1 to 2 liters) often cause surprisingly little disturbance. If, however, the pericardium is thickened due to previous inflammation, small quantities of fluid may produce the effect of tamponade.

these circumstances relatively small quantities of blood may prove fatal. The pericardium or the veins are not dilated to any marked degree since this process requires time. The picture is, therefore, different from that of a slowly accumulating fluid with extreme dilatation.²⁵⁸

Cholesterol Pericarditis.—Rarely, cholesterol crystals are present in the pericardial fluid. Tamponade may be present²⁶² or there may be only small quantities of inspissated exudate loaded with golden flecks of cholesterol. Tuberculosis has been suspected as a cause, also hemorrhage.²⁶³



Fig. 387.—Hemopericardium due to rupture of aneurysm into pericardial sac. (Courtesy Dr. H. C. Schmeisser. From Anderson, Synopsis of Pathology.)

Hemopericardium.—Blood in the pericardial sac occurs in a wide variety of conditions. Common causes are ruptured aneurysms of the ascending aorta or its arch, penetrating wounds of the heart, acute infections of the pericardium, metastatic carcinoma, and scurvy. Hemorrhage from a recent infarction of the wall of the left ventricle is common but usually small in amount. Rupture of the heart, which results chiefly from acute myocardial infarction but also from acute infections, contusions, and penetrating wounds, often produces very rapid or instantaneous tamponade. Under

Pericarditis

Fibrinous and Serofibrinous Pericarditis.—Fibrinous exudate over the pericardial surfaces is seen frequently and under a variety of conditions. The exudate may be thin, dry or moist, shaggy, villous, or like "bread and butter." Frequently it consists of a thin film covering only part of the pericardial surfaces. It is clinically manifest by the presence of a friction rub. The usual causes of fibrinous pericarditis are rheumatic fever, infections with pyogenic cocci, tuberculosis, and uremia. When due to acute infections, serous effusion often accom-

panies the laying down of fibrin, thus introducing symptoms of tamponade. The serous fluid contains more albumin than the transudates discussed previously, has a greater specific gravity, and may coagulate on standing. Organisms gain access to the pericardium through the blood stream, by direct extension from a contiguous abscess, from empyema, or a caseous tuberculous lymph node. Pneumonitis in the left lower lobe sometimes gives rise to pericarditis.

in these denuded areas, thus becoming attached directly to the subendothelial connective tissue. The capillaries of the loose connective tissue become engorged with blood, and edema is nearly always present. Polymorphonuclear leukocytes are found sparsely scattered throughout the wall and often form a barrier just below the fibrin deposits.

Rheumatic pericarditis is a common accompaniment of rheumatic fever. It may be the sole cardiac lesion but more frequently is part



Fig. 388.—Acute fibrinous pericarditis. Note the shaggy coat of fibrin covering the surface of the heart. (Courtesy Dr. H. C. Schmeisser. From Anderson, Synopsis of Pathology.)

Serous inflammation causes the pericardial surfaces to lose their glistening sheen and assume a dull, opaque appearance. Many of the lining cells undergo swelling and show granular or fatty degeneration. Many of the cells are desquamated, and fibrin becomes deposited

of a pancarditis. The exudate varies from a thin film of fibrin to a heavy, shaggy coat. Serofibrinous effusions of 200 to 800 c.c. may be encountered, and, rarely, even up to 1,200 c.c.²⁶⁴ Of 135 patients who died of rheumatic fever, autopsy revealed acute pericarditis in 55 per cent and evidence of chronic involvement of the pericardium in another 25 per cent.²⁶⁴ In rheumatic pericarditis, lymphocytes, eosino-

philes, and large mononuclear cells are more abundant in the pericardial wall than polymorphonuclear leukocytes. Aschoff bodies are often seen in the epicardium. If much fluid is present (transudate), recovery may occur without pericardial adhesions. Abundant fibrin, on the other hand, attracts fibroblasts, and adhesive pericarditis is the usual result.

Uremic Pericarditis.—In persons dying in uremia, the pericardial surfaces are frequently covered by a thin film of fibrin. Occasionally the coat may be fairly thick, but the amount of fluid is not large. A friction rub is generally present.²⁵⁸ Occasionally, ubiquitous diplo-streptococci are present, but in the majority of instances the exudate is sterile. The cause of the condition is unknown.

pericardium. *Streptococcus pyogenes* is less frequently the infecting organism. When it does occur, it is a severe, often fatal disease, unless recognized early and treated. In these days of chemotherapy the incidence is probably low. Besides the manifestations of severe acute infection, symptoms of cardiac tamponade are out of proportion to the amount of exudate present. Inflammation and edematous thickening of the wall interfere, no doubt, with the usual degree of stretching. Surgical drainage should be undertaken when



Fig. 389. Chronic adhesive pericarditis. The pericardial sac has been opened, displaying the fibrous bands joining visceral and parietal pericardium (Courtesy Dr. H. C. Schmeisser. From Anderson, Synopsis of Pathology.)

Purulent pericarditis is, at times, a complication of pneumococcus pneumonia, or osteomyelitis due to *Staphylococcus aureus*. Penetrating wounds of the heart are frequently followed by staphylococcal infections with pus accumulating in the

the diagnosis is made, supported by penicillin or other bacteriostatics. On inspection, the surface is covered with a yellowish or a slimy gray layer of exudate. If much fibrin is present, the layer is thick, shaggy, and gelatinous. Microscopically,

many polymorphonuclear leukocytes are observed throughout the pericardial wall. A compact layer of similar cells in various stages of degeneration are deposited on the surface and enmeshed in the network of fibrin.

Chronic Adhesive Pericarditis.—Fibrinous exudates exhibit a decided tendency to undergo organization, probably due to a chemotactic influence exerted on the connective tissue cells. As the fibroblasts penetrate the fibrin, they dissolve it, forming a vascular granulation tissue with islands of denser fibrinous deposits remaining here and there. In places where the surface endothelium has not been destroyed the cells become cuboidal and may form ductlike structures. As organization progresses, the connective tissue matures, forming tough scar tissue, binding the two layers of the pericardium firmly together. The cavity may be completely obliterated, or pockets of varying sizes may remain where organization failed because of thinness of the exudate. Fibrinopurulent exudates on organization may produce very dense, thick fibrous walls. This condition should not be confused with chronic constrictive pericarditis since there is usually little or no embarrassment of the heart.

Granulomatous Infections of the Pericardium

Tuberculosis of the Pericardium.—Pericarditis due to *Mycobacterium tuberculosis* is the least common but the most serious of the tuberculous infections of the serous membranes.²⁶⁵ The macroscopic appearance is that of enlargement and thickening of the pericardium. The parietal layer is thickened and leathery and often contains gray nodules. The visceral layer is covered with a thick, shaggy blood-stained fibrin, often arranged in ridges due to the contractions of the heart. The deeper layers of fibrin are usually undergoing organization. Grayish tubercles may be seen in this layer and in the thickened epicardium. Occasionally, caseous areas coalesce to form a yellowish-white interrupted layer. Effusion of fluid may occur soon after fibrin formation. The amount of fluid varies from a few hundred cubic centimeters to as much as 3.5 liters.²⁶⁶ As might be expected, cardiac tamponade is the cause of death in some instances. The tuberculous pericarditis due to hematogenous spread as part of a miliary tuberculosis produces miliary nodules in the pericardium accompanied by small effusions.²⁶⁷ More frequently, infection is the result of lymphatic spread from caseous lymph nodes in the mediastinum. In one-third to one-half of the cases reported by Keefer,²⁶⁵ Harvey and Whitehill,²⁶⁶ caseous lymph nodes were

present in the adjacent tissues. Occasionally a caseous node ulcerates into the pericardium. Many tubercle bacilli are thus introduced into the pericardial sac, together with much tuberculo-protein from broken-down bacilli. Large inflammatory exudates result since the tissues are usually highly sensitized to this substance.²⁶⁷ Tuberculous pericarditis is found uncommonly in chronic pulmonary tuberculosis in the white race, probably because the tracheobronchial lymph nodes are usually not involved in this form of the disease.²⁶⁸ In the Negro race, tuberculosis tends to be fulminating with abundant caseation, liquefaction, and lymph node involvement.²⁶⁷ Under these circumstances tuberculous pericarditis is more common.

Actinomycosis of Pericardium.—In congestive heart failure due to actinomycosis, pericarditis plays the major role.²⁶⁸ Seventy cases of cardiac actinomycosis have been reported to 1944. The infection extends to the pericardium most often from actinomycosis of the lungs. In 15 of 24 cases in which the details are given, the pericardial sac was completely obliterated. Effusion occurs rarely. The two layers of the pericardium were thickened, as a rule, by actinomycotic granulation tissue in which suppurative foci occurred.

Coccidioidomycosis of the pericardium is an extremely rare condition. In a case seen recently at the Los Angeles County Hospital, the heart and pericardium together weighed 1,000 grams. Clinically and pathologically the condition resembled tuberculous pericarditis and was so diagnosed at the autopsy table.

Constrictive Pericarditis

Chronic constrictive pericarditis, formerly called **Pick's disease**,²⁶⁹ is that condition in which fibrous thickening of the pericardium mechanically interferes with the heart action and the circulation. According to Burwell and Blalock,²⁷⁰ pressure in the veins is increased to about three times normal, while arterial pressure and pulse pressure are moderately reduced. The heart speeds up, but the output of the heart per minute and the velocity of the blood flow are diminished. Total blood volume is increased as in congestive heart failure. The dense fibrous tissue of the pericardium narrows the orifices of the vena cavae tending to back up the blood in the venous system. This produces so-called "inflow-stasis" and waterlogging of tissues. The hepatic veins likewise may be narrowed where they enter the inferior vena cava. A pseudocirrhosis with ascites is usually ushered in by this condition (Pick's disease).²⁶⁹ (Fig. 392.) **Polyserositis (Concato's disease)** is characterized by large effusions into the various serous cavities:

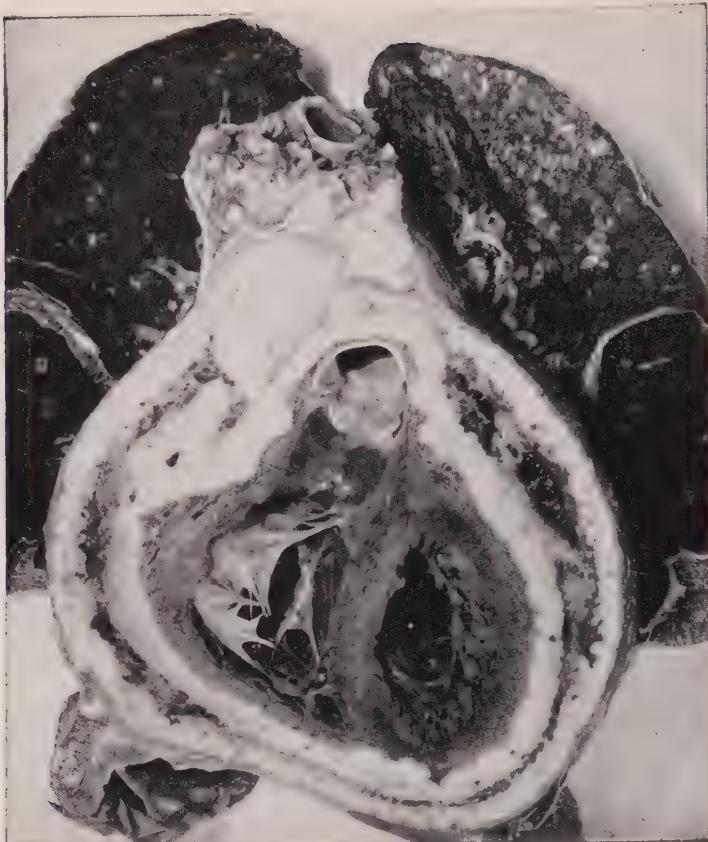


Fig. 390.—Tuberculous pericarditis. Note the tremendous thickening of visceral and parietal pericardium, the massive caseation of the mediastinal lymph nodes, and the tuberculous areas in lung tissue. (Courtesy Dr. H. C. Schmeisser. From Anderson, *Synopsis of Pathology*.)

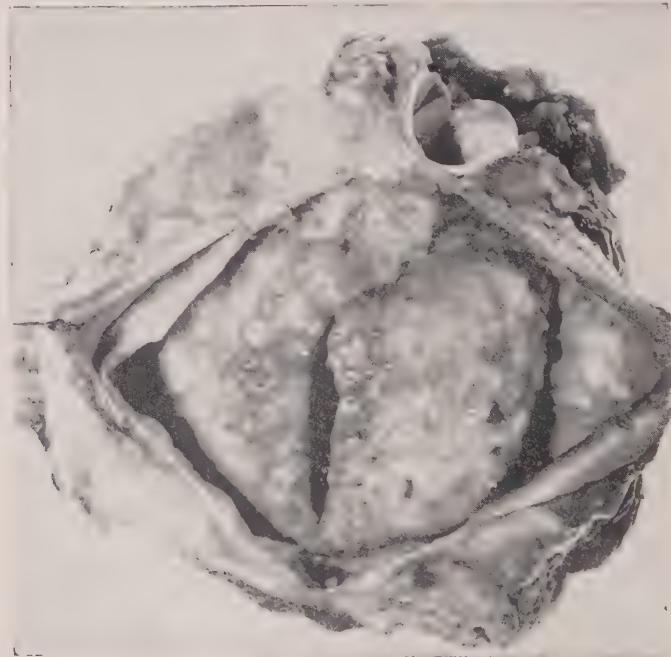


Fig. 391.—Healing tuberculous pericarditis. The roughened epicardium is covered with organizing fibrin, parietal pericardium thickened. White man, 51 years old. Heart and pericardium weighed 930 grams.

the pericardium, pleurae, and peritoneum. This syndrome often terminates in constrictive pericarditis, with chronic perihepatitis and perisplenitis ("cake icing" of liver and spleen).

Chronic constrictive pericarditis is most often tuberculous in origin and may follow a tuberculous polyserositis.²⁷¹ Occasionally, it is caused by other bacterial and granulomatous infections.

Rheumatic fever does not appear to be a factor. Pericardectomy for relief of

studies and physical signs it is believed that these extensive adhesions interfere with the cardiac contractions and thus add to the work of the heart. This burden is a continuous one and is, therefore, thought to be effective in producing cardiac hypertrophy demonstrated in these patients, as well as heart failure which is a common sequence.²⁵⁸ Many of these patients exhibit old valvular lesions, added factors in hypertrophy and congestive failure, and evidence supporting the generally accepted rheumatic etiology.

Calcification of the pericardium is observed occasionally. Calcium salts may be deposited as isolated concretions, as thin, eggshell-like

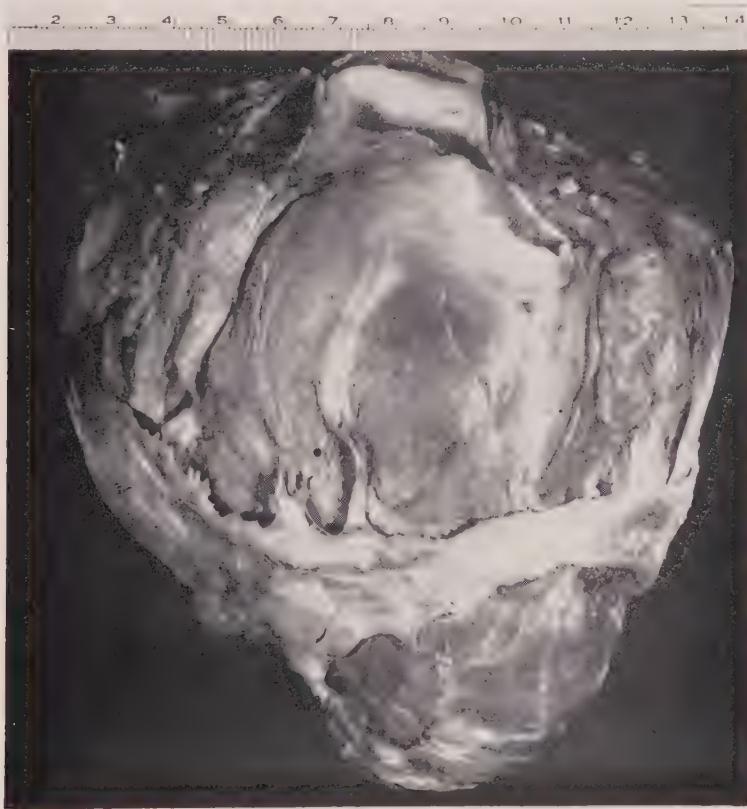


Fig. 392.—Constrictive pericarditis. Note the band of calcified tissue (6 to 1.5 cm. in width) which definitely constricts the heart. The thickened fibrous pericardium which covered the rest of the heart has been removed. White woman, 38 years old, with marked recurring ascites.

constrictive pericarditis has now become an established procedure. Cures ranging from 50 to 70 per cent of operative cases have been reported.^{272, 273}

Mediastinopericarditis.—A less common syndrome simulating constrictive pericarditis in many respects is known as mediastinopericarditis. This is a chronic fibrous pericarditis in which the heart and pericardium are firmly bound to contiguous structures such as the sternum, ribs, pleurae, diaphragm, and mediastinal tissues. On the basis of anatomical

flakes, or as a fairly extensive encrustation of the wall. In the latter case, symptoms of constrictive pericarditis are to be expected. The condition is more common among older persons and appears to be associated with infections. Association with an old tuberculosis of the pericardium is most common. The residue of a purulent pericarditis may at times calcify. Diagnosis can be readily made by x-ray examination,²⁵⁸ (Fig. 392).

Trauma of the Pericardium.—Penetrating, stab or bullet wounds are the more common sources of traumatic injury to the pericardium.^{274, 275}

Tumors of the Pericardium

Primary tumors of the pericardium are very rare. Among benign tumors, lipomas, lobulated fibrous polyps and hemangiomas have been mentioned.²⁷⁶ Yater²⁷⁶ found in the literature 45 sarcomas affecting the heart, of which 10 were listed as arising from the pericardium. Several instances of primary mesotheliomas of the pericardium have been described. These apparently arise from the lining endothelium. Secondary tumors of the pericardium are similar to those described as affecting the heart. Lymphoblastomas derived from cervical or mediastinal lymph nodes at times produce a thick, boardlike infiltration of the parietal layer, especially, and the visceral layer overlying the auricles.²⁷⁷

References

Pathologic Physiology of Heart Failure

- Starling, E. H.: The Linacre Lecture on The Law of the Heart, London, 1918, p. 26.
- Warren, James V., and Stead, Eugene A., Jr.: Arch. Int. Med. 73: 138, 1944.
- Harrison, Tinsley Randolph: Failure of the Circulation, ed. 2, Baltimore, 1939, Williams & Wilkins Co.

Rheumatic Fever and Rheumatic Heart Disease

General

- Griffith, G. C.: J. A. M. A. 133: 974, 1947.
- Forbus, Wiley D.: Reaction to Injury, Baltimore, 1943, Williams & Wilkins Co.

Incidence and Epidemiology

- Chavez, Ignacio: Am. Heart J. 24: 88, 1942.
- Coburn, A. F.: Lancet 2: 1025, 1936.
- Dublin, T. D.: Modern Concepts of Cardiovascular Disease 13, No. 7, July, 1944, New York, American Heart Association.

Race

- Vesey, John M.: U. S. Naval Med. Bull. 47: 805, 1947.

Heredity

- Wilson, M. G., Schweitzer, M. D., and Lubiszew, R.: J. Pediat. 22: 468, 581, 1943.

Environment

- Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. American Heart Association, 1943, Printed by Metropolitan Life Insurance Co. (Fig. 10).
- Clarke, P. J.: Irish J. M. Sc. 97: 75, 1940.

Etiology

- Weintraub, W.: Berl. Klin. Wchnschr. 50: 1381, 1913.
- Zinsser, H.: Bull. New York Acad. Med. 4: 351, 1928.
- Swift, H. F., Derick, C. L., and Hitchcock, C. H.: Tr. A. Am. Phys. 43: 192, 1928.
- Swift, H. F.: J. A. M. A. 92: 2071, 1929.
- Glover, J. A.: Lancet 1: 499, 1930.
- Coburn, A. F., and Pauli, Ruth H.: J. Exper. Med. 56: 609, 1932.

- Lancefield, R. C.: J. Exper. Med. 47: 91, 1928.
- Lancefield, R. C.: J. Exper. Med. 57: 571, 1933.
- Griffith, F.: J. Hyg. 34: 542, 1934.
- Huntington, R. W., Jr., Comdr. (M.C.) U. S. N.: Personal communication.

- Grishaw, W. H., Maj. (M.C.) A. U. S.: Personal communication.
- Fischel, Edw. E., and Pauli, Ruth H.: J. Exper. Med. 89: 669, 1949.
- McKeown, E. Florence: J. Path. & Bact. 59: 547, 1947.

- Murphy, Geo. E., and Swift, Homer F.: J. Exper. Med. 89: 687, 1949; 91: 485, 1950.

Immunity

- Coburn, A. F., and Pauli, Ruth H.: J. Exper. Med. 56: 651, 1932.
- Todd, E. W.: Brit. J. Exper. Path. 13: 248, 1932.
- Swift, H. F., and McEwen, C.: Oxford Med. V, Part I, New York, 1940, Oxford University Press.
- Swift, H. F., and Hodge, B. E.: Proc. Soc. Exper. Biol. & Med. 34: 849, 1936.
- Coburn, A. F.: Lancet 2: 1025, 1936.

Basic Pathologic Change, Aschoff Body

- Neumann, E.: Arch. f. mikr. Anat. 18: 130, 1880.
- Klinge, F.: Der Rheumatismus, Pathologisch-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für das ärztliche Rheumaproblem. Ergebn. d. allg. Path. u. path. Anat. 27: 1-354, 1933 (monograph).
- Klinge, F.: Virchows Arch. 278: 438, 1930 (acute phase).
- Klinge, F.: Virchows Arch 279: 1, 1930 (proliferative phase).
- Klinge, F.: Virchows Arch. 279: 16, 1930 (scarring).
- Murphy, G. E.: J. Exper. Med. 95: 319, 1952.
- Baitsell, G. A.: Am. J. Physiol. 44: 109, 1917.
- Hass, G., and McDonald, F.: Am. J. Path. 16: 525, 1940.
- Wolbach, S. B., and Howe, P. R.: Arch. Path. 1: 1-24, 1926.
- Meyer, K., and Rapport, M. M.: Science 113: 596, 1951.
- Meyer, K.: Physiol. Rev. 27: 335, 1947.
- Altshuler, Chas. H., and Angevine, D. M.: Am. J. Path. 25: 1061, 1949.
- Dougherty, Thos. F., and Schnubeli, G. L.: Proc. Exper. Biol. & Med. 15: 854, 1950.
- Benditt, E. P., Schiller, Sara, Wong, Helen, and Dorfman, A.: Proc. Exper. Biol. & Med. 75: 782, 1950.
- Aschoff, L.: Verhandl. d. deutsch. path. Gesellsch 8: 46, 1905.
- Gross, Louis, and Ehrlich, Joseph C.: Am. J. Path. 10: 467, 1934.
- McEwen, Currier: J. Exper. Med. 55: 745, 1932.
- Clawson, B. J.: Arch. Path. 32: 760, 1941.
- Wilson, M. G., Wheeler, G. W., and Leask, M.: J. Clin. Investigation 14: 333, 1935.
- Clawson, B. J., Noble, J. F., and Lufkin, N. H.: Am. Heart J. 15: 58, 1938.
- Hall, E. M., and Ichioka, T.: Am. J. Path. 16: 761, 1940.
- Keil, H.: Medicine 17: 261, 1938 (subcutaneous nodule).
- Massell, B. F., Coen, W. D., and Jones, T. D.: Pediatrics 5: 909, 1950.
- Leary, T.: Arch. Path. 13: 1, 1932 (rheumatic endocarditis).
- Saphir, O.: Arch. Path. 32: 1000, 1941; and 33: 88, 1942 (rheumatic myocarditis).
- Pappenheimer, A. M., and Von Glahn, W. C.: J. Med. Research 54: 489, 1924 (rheumatic aortitis).
- Von Glahn, W. C., and Pappenheimer, A. M.: Am. J. Path. 2: 235, 1926 (rheumatic arteritis).
- Karsner, H. T., and Bayless, F.: Am. Heart J. 9: 557, 1934.
- Gross, L., Kugel, M. A., and Epstein, E. Z.: Am. J. Path. 11: 253, 1935.
- Fahr, T.: Virchows Arch. f. path. Anat. 232: 134, 1921 (rheumatic arthritis).
- Paul, J. R.: Medicine 7: 383, 1928 (pleural and pulmonary lesions).
- Jensen, C. R.: Arch. Int. Med. 77: 237, 1946.
- Griffith, Geo. C., Phillips, A. W., and Asher, Curtis: Am. J. M. Sc. 212: 22, 1946.

Chorea

- MacIntosh, A. W., and Anderson, A. G.: Chorea, Oxford Med. VI, Part III, New York, 1940, Oxford University Press, p. 937.
- Sturgis, O.: Quoted by MacIntosh and Anderson.²⁷⁸
- Barnes, Arlie R.: Circulation 3: 770, 1951.
- Massell, B. F., Warren, J. E., Sturgis, G. P., Hall, E., and Craige, E.: N. England J. Med. 242: 692, 1950.

Syphilitic Heart Disease

66. Saphir, O., and Scott, R. W.: Am. J. Path. 3: 527, 1927.

*Valvular Deformities**General*

67. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: Am. J. Path. 2: 193, 1926.

Mitral Stenosis

68. MacCallum, W. G.: Bull. Johns Hopkins Hosp. 35: 329, 1925.

Aortic Stenosis

69. Clawson, B. J., Noble, J. F., and Lufkin, N. H.: Am. Heart J. 15: 58, 1938.

70. Dry, T. J., and Willius, F. A.: Am. Heart J. 17: 138, 1939.

71. Hall, E. M., and Ichioka, T.: Am. J. Path. 16: 761, 1940.

72. Karsner, H. T., and Koletsky, S.: Tr. A. Am. Physicians 55: 188, 1940.

73. Mönckeberg, J. G.: Virchows Arch. f. path. Anat. 176: 472, 1904.

Tricuspid Valvular Disease

74. Smith, J. A., and Levine, S. A.: Am. Heart J. 23: 739, 1942.

Pulmonary Valvular Disease

75. McGuire, J., and McNamara, R. J.: Am. Heart J. 14: 562, 1937.

Bacterial Endocarditis

76. von Glahn, W. C., and Pappenheimer, A. M.: Arch. Int. Med. 55: 173, 1935.

77. Abbott, M. E.: Ann. Clin. Med. 4: 189, 1925.

78. Wearn, J. T., Bromer, A. W., and Zschiesche, L. J.: Am. Heart J. 11: 22, 1936 (blood vessels in valves).

79. Gross, L.: Am. Heart J. 13: 275, 1937 (blood vessels in valves).

80. Weiss, H.: Arch. Int. Med. 54: 710, 1934.

81. Kelson, S. R., and White, P. D.: Ann. Int. Med. 22: 40, 1945.

82. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Co.

83. Blumer, G.: Medicine 2: 105, 1923.

84. Moore, R. A.: J. Lab. & Clin. Med. 31: 1279, 1946.

85. Friedman, M., Katz, L. N., Howell, K., Lindner, E., and Mendlowitz, M.: Arch. Int. Med. 61: 95, 1938.

86. Clawson, B. J.: Arch. Int. Med. 33: 157, 1924 (embolic lesions).

87. Keefer, S.: Ann. Int. Med. 11: 714, 1937-38.

88. Hamman, L., and Rienhoff, W. F., Jr.: Bull. Johns Hopkins Hosp. 57: 219, 1935.

89. Keys, A., and Shapiro, M. J.: Am. Heart J. 25: 158, 1943.

90. Friedberg, Charles K.: J. A. M. A. 144: 527, 1950.

Nonbacterial Thrombotic Endocarditis

91. Libman, E.: J. A. M. A. 80: 813, 1923.

92. Gross, L., and Friedberg, C. K.: Arch. Int. Med. 58: 620, 1936.

93. Allen, A. C., and Sirota, J. H.: Am. J. Path. 20: 1025, 1944.

*Atypical Verrucous Endocarditis
(Libman-Sacks)*

94. Libman, E., and Sacks, B.: Arch. Int. Med. 33: 701, 1924.

95. Gross, L.: Libman Anniversary Volumes, New York International Press, 2: 527, 1932.

Tuberculous Endocarditis

96. Baker, R. D.: Arch. Path. 19: 611, 1935.

Other Granulomatous Forms of Endocarditis

97. Cornell, A., and Shookhoff, H. B.: Arch. Int. Med. 74: 11, 1944.

98. Beamer, P. R., Reinhard, E. H., and Goodof, I. I.: Am. Heart J. 29: 99, 1945.

99. Broders, A. C., Dochat, G. R., Herrell, W. E., and Vaughn, L. D.: J. A. M. A. 122: 489, 1943.

100. Russell, W. O., and Lamb, M. E.: J. A. M. A. 114: 1045, 1940.

101. Klauder, J. V., Kramer, D. W., and Nicholas, L.: J. A. M. A. 122: 938, 1943.

*Lesions of the Myocardium**Fatty Degeneration*

102. Kaufmann, E.: Pathology (English Translation by S. P. Reimann), Philadelphia, 1929, P. Blakiston's Sons & Co.

103. Dibble, J. H., and Gerrard, W. W.: J. Path. & Bact. 46: 77, 1938.

Glycogen Infiltration

104. Van Creveld, S.: Medicine 18: 1, 1939.

Myocarditis, Acute Infectious

105. Saphir, O.: Arch. Path. 32: 1000, 1941; 33: 88, 1942.

106. Gore, Ira, and Saphir, O.: Am. Heart J. 34: 829, 1947.

107. Burkhardt, E. A., Eggleston, C., and Smith, L. W.: Am. J. M. Sc. 195: 301, 1938.

108. Gulkelberg, M.: Quoted from Saphir,¹⁰⁵ p. 1010.

109. Martin, D. S., and Smith, D. T.: Am. Rev. Tuberc. 39: 275, 1939.

110. Kasper, J. A., and Pinner, M.: Arch. Path. 10: 687, 1930.

Myocarditis in Typhus

111. Wolbach, S. B., Todd, J. R., and Palfrey, F. W.: The Etiology and Pathology of Typhus, Cambridge, Mass., 1922, Harvard University Press.

112. Herzog, E., and Rodriguez, H.: Quoted from Saphir: Arch. Path. 33: 106, 1942.

Toxic Myocarditis

113. Beck, H. G., and Suter, G. M.: J. A. M. A. 110: 1982, 1938.

114. Neuburger, K. T., and Clarke, E. R.: Rocky Mountain J. M. 42: 29, 1945.

115. Haggard, H. W.: Am. J. Physiol. 56: 390, 1921.

116. French, A. J., and Weller, C. V.: Am. J. Path. 18: 109, 1942.

117. More, Robt. H., McMillan, G. C., and Duff, G. L.: Am. J. Path. 22: 703, 1946.

118. Simon, M. A.: Am. J. M. Sc. 205: 439, 1943.

119. Fawcett, Robt. M.: Arch. Path. 45: 25, 1948.

Isolated Myocarditis

120. Fiedler: Ueber akute interstitielle Myocarditis in Festschrift des 4 stadtkrankhauses, Dresden-Friedrichstadt, 1899 (cited by Saphir¹⁰⁵).

Myocarditis in Bacterial Endocarditis

121. Saphir, O., Katz, L. N., and Gore, Ira: Circulation 1: 1155, 1950.

122. Libman, E.: J. A. M. A. 80: 813, 1923.

Syphilitic Myocarditis

123. Spain, D. M., and Johannsen, M. W.: Am. Heart J. 24: 689, 1942.

124. Warthin, A. S.: Am. J. M. Sc. 147: 667, 1914.

Tuberculous Myocarditis

125. Gouley, B. A., Bellet, S., and McMillan, T. M.: Arch. Int. Med. 51: 244, 1933.

126. Horn, H., and Saphir, O.: Am. Rev. Tuberc. 32: 492, 1935.

Sarcoidosis of Myocardium

127. Longcope, W. T., and Fisher, A. M.: J. Mt. Sinai Hosp. 8: 784, 1941-42.

128. Nickerson, D. A.: Arch. Path. 24: 19, 1937.

Myocarditis in Chagas' Disease

129. Chagas, C.: Mem. Inst. Oswaldo Cruz, Rio de Janeiro 1: 158, 1909 (cited by Wood and Wood¹²⁰).

130. Wood, F. D., and Wood, S. F.: Am. J. Trop. Med. 21: 335, 1941.

Myocarditis in Toxoplasmosis

131. Pinkerton, H., and Weinman, D.: Arch. Path. 30: 374, 1940.

132. Pinkerton, H., and Henderson, R. G.: J. A. M. A. **116**: 807, 1941.

Myocarditis in Trichinosis

133. Dunlap, G. L., and Weiller, C. V.: Proc. Soc. Exper. Biol. & Med. **30**: 1261, 1932-1933.
134. Spink, W. W.: Arch. Int. Med. **56**: 238, 1935.

Intestinal Parasites in Myocardium

135. Craig, C. F., and Faust, E. C.: Clinical Parasitology, Philadelphia, 1940, Lea & Febiger.

Trauma

136. Beck, C. S.: J. A. M. A. **104**: 109, 1935.
137. Kellert, E.: J. Lab. & Clin. Med. **2**: 726, 1917.
138. Copeland, G.: J. A. M. A. **63**: 1950, 1914.
139. Bright, E. F., and Beck, C. S.: Am. Heart J. **10**: 293, 1934-35.

Circulatory Disturbances of the Heart

Anatomy of Coronary Arteries

140. Whitten, M. B.: Arch. Int. Med. **45**: 383, 1930.
141. Gross, L.: Blood Supply to the Heart, New York, 1921, Paul B. Hoeber, Inc.
142. Dock, W.: J. A. M. A. **131**: 875, 1946.
143. Fangman, R. J., and Hellwig, C. A.: Am. J. Path. **23**: 901, 1947 (histology of coronary arteries in newborn infants).
144. Lack, A. R.: The Coronary Arteries in the Newborn and in Childhood. Read before the Joint Meeting of Sections on General Surgery, Radiology and General Practice, Forty-fourth Annual Meeting of Calif. Med. Ass., Los Angeles, May 1, 1947.
145. Prinzmetal, M., Simkin, B., Bergman, H. C., and Kruger, H. E.: Am. Heart J. **33**: 420, 1947.

Coronary Occlusion

146. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Am. Heart J. **19**: 1, 1940.
147. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: J. A. M. A. **116**: 91, 1941.
148. Schlesinger, M. J.: Am. Heart J. **15**: 528, 1938.
149. Levine, S. A.: The Prognosis of Coronary Occlusion. Pt. I. Modern Concepts of Cardio-Vascular Disease. XI, No. 5, 1942, New York, American Heart Association.

Etiology of Coronary Disease

150. Glendy, R. E., Levine, S. A., and White, P. D.: J. A. M. A. **109**: 1775, 1937.
151. Plotz, Milton: J. A. M. A. **139**: 623, 1949.
152. Gofman, J. W., Lindgren, F., Elliott, H., Mantz, W., Hewitt, J., Strisower, B., and Herring, V.: Science **111**: 166, 1950; Am. J. Med. **11**: 358, 1951.
153. Yater, W. M., and others: Am. Heart J. **36**: 334, 1948.
154. Bell, E. T., and Clawson, B. J.: Arch. Path. **5**: 939, 1928.

Coronary Sclerosis

155. Master, A. M., Dock, S., Horn, H., Freedman, B. I., and Field, L. E.: Circulation **1**: 1302, 1950.
156. Schlesinger, M. J., and Zoll, P. M.: Arch. Path. **32**: 178, 1941.

Coronary Thrombosis

157. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Am. Heart J. **10**: 567, 762, 1934-35.
158. Duguid, J. B.: J. Path. & Bact. **58**: 207, 1946.

Intramural Hemorrhage

159. Winternitz, M. C., Thomas, R. M., and Le Compte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., 1938, Charles C. Thomas.
160. Wartman, W. B.: Am. Heart J. **15**: 459, 1938.

Coronary Embolism

161. Moraques, V., Bawell, M. B., and Shrader, E. L.: Circulation **2**: 434, 1950.
162. Garvin, C. F., and Work, J. L.: Am. Heart J. **18**: 747, 1939.

Xanthomatosis

163. Muller, C.: Arch. Int. Med. **64**: 675, 1939.
Buerger's Disease
164. Allen, E. V., and Willius, F. A.: Ann. Int. Med. **3**: 35, 1929.

Myocardial Infarction

165. Gross, H., and Sternberg, W. H.: Arch. Int. Med. **64**: 249, 1939.
166. Mallory, G. K., White, P. D., and Salcedo-Salgar, J.: Am. Heart J. **18**: 647, 1939.

Rupture of the Heart

167. Krumbhaar, E. B., and Crowell, C.: Am. J. M. Sc. **170**: 828, 1925.
168. Edmondson, H. A., and Hoxie, H. J.: Am. Heart J. **24**: 719, 1942.

Aneurysm of the Heart

169. Crawford, J. H.: Arch. Int. Med. **71**: 502, 1943.

Pathology of Sudden Death

170. Weiss, Soma: N. England J. Med. **223**: 793, 1940.
171. Martland, H. S.: Unpublished data quoted by Soma Weiss.¹⁷⁰
172. Hamman, L.: Bull. Johns Hopkins Hosp. **55**: 387, 1934.

Pathological Basis of Angina Pectoris

173. Keefer, C. S., and Resnik, W. H.: Arch. Int. Med. **41**: 769, 1928.
174. Harrison, T. R.: Failure of the Circulation. Baltimore, 1939, Williams & Wilkins Co.
175. Beck, C. S.: Ann. Surg. **102**: 801, 1935; and J. A. M. A. **137**: 436, 1948.
176. Feil, H., and Beck, C. S.: J. Thoracic Surg. **10**: 529, 1940-41.

Conduction System of the Heart

177. Wolff, L., Parkinson, J., and White, P. D.: Am. Heart J. **5**: 685, 1929-1930.
178. Wood, F. C., Wolfirth, C. C., and Geckeler, G. D.: Am. Heart J. **25**: 454, 1943.
179. Butterworth, J. S., and Poindexter, C. A.: Am. Heart J. **28**: 149, 1944.
180. Yater, W. M., and Cornell, V. H.: Ann. Int. Med. **8**: 777, 1935.

Abnormalities in Size of Heart

181. Symmers, D.: Am. J. M. Sc. **156**: 40, 1918 (hypoplasia).
182. Karsner, H. T., Saphir, O., and Todd, T. W.: Am. J. Path. **1**: 351, 1925 (atrophy).

Hypertrophy and Dilatation

183. Harrison, T. R.: Failure of the Circulation. Baltimore, 1939, Williams & Wilkins Co., p. 158.
184. Spain, D. M., and Handler, B. J.: Arch. Int. Med. **77**: 37, 1946.

Pathogenesis of Arterial Hypertension

185. Page, I. H., and Corcoran, A. C.: Arterial Hypertension. Its Diagnosis and Treatment, Chicago, 1945, The Yearbook Publishers, Inc.
186. Landis, E. M.: Essential Hypertension I. Modern Concepts of Cardiovascular Disease XII, August, 1943.
187. Bright, Richard: Cases and Observations Illustrative of Renal Disease. Guy's Hosp. Rep. **1**: 338, 1836.
188. Goldblatt, H., Lynch, Jas., Hanzal, R. F., and Summerville, W. W.: J. Exper. Med. **59**: 347, 1934.
189. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia. Harvey Lectures, 1937-38.
190. Page, I. H., and Helmer, O. M.: J. Exper. Med. **71**: 29, 1940.
191. Houssay, B. A., and Braun-Menendez, E.: Brit. M. J. **2**: 179, 1942.
192. Moritz, A. R., and Oldt, M. R.: Am. J. Path. **13**: 679, 1937.
193. Castleman, B., and Smithwick, R. H.: J. A. M. A. **121**: 1256, 1943, and New England J. M. **239**: 729, 1948.

Hypertensive Heart Disease

194. Clawson, B. J.: Am. Heart J. 22: 607, 1941.

*Miscellaneous Cardiac Disturbances**Beriberi Heart*

195. Weiss, S., and Wilkens, R. W.: Ann. Int. Med. 11: 104, 1937-1938.

196. Dock, Wm.: Tr. A. Am. Physicians 55: 61, 1940.

The Heart in Hyperthyroidism

197. Likoff, W. B., and Levine, S. A.: Am. J. M. Sc. 206: 425, 1943.

The Heart in Myxedema

198. Higgins, W. H.: Am. J. M. Sc. 191: 80, 1936.

199. Willius, F. A., and Haines, S. F.: Am. Heart J. 1: 67, 1925.

*The Heart in Acromegaly*200. Huchard, H.: Cited by Courville and Mason.²⁰¹

201. Courville, C., and Mason, V. R.: Arch. Int. Med. 61: 704, 1938.

The Heart in Anemia

202. Harrison, T. R.: Failure of the Circulation, Baltimore, 1939, Williams & Wilkins Co., pp. 421-423.

203. Ellis, L. B., and Faulkner, J. M.: New England J. Med. 220: 943, 1939.

204. Ball, D.: Am. Heart J. 6: 517, 1930-1931.

205. Elliott, A. H.: Am. J. M. Sc. 187: 185, 1934.

Tumors of the Heart

206. Straus, R., and Merliss, R.: Arch. Path. 39: 74, 1945.

207. Yater, W. M.: Arch. Int. Med. 48: 627, 1931.

208. Husten, K.: Quoted from Yater.²⁰⁷

209. Taussig, Helen: Congenital Heart Disease, New York, 1947, The Commonwealth Fund, pp. 357-358.

210. Walker, G. C., and Ellis, L. B.: Proc. New England Ht. Ass'n, p. 26, 1940-41.

211. Abbott, M. E.: Nelson's New Loose Leaf Medicine, Thos. Nelson & Sons, 4: 207-321, 1941.

212. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.

*Congenital Heart Disease**General*

213. Gregg, N. McAlister: Tr. Ophth. Soc. Australia (Brit. Med. Ass.) 3: 35, 1941.

214. Swan, Charles, Tostevin, A. L., Moore, Brian, Mayo, Helen, and Barham Black, G. H.: M. J. Australia 2: 201, 1943.

215. Butt, E. M., and Simonsen, D. G.: Am. J. Path. 20: 716, 1950.

216. Clawson, B. J.: Text-Book of Pathology, E. T. Bell, ed. 5, Philadelphia, 1944, Lea & Febiger.

217. Robey, W. H.: Nation's Health 9: 21, 1927.

Dextrocardia

218. Le Wald, L. T.: J. A. M. A. 84: 261, 1925.

219. Rosler, H.: Wien. Arch. f. inn. Med. 19: 505, 1930.

Idiopathic Hypertrophy

220. Stoloff, E. G.: Am. J. Dis. Child. 36: 1204, 1928.

221. Rosen, A. N.: Am. J. Dis. Child. 65: 905, 1943.

Congenital Rhabdomyoma

222. Rehder, H.: Virchows Arch. f. path. Anat. 217: 174, 1914.

223. Farber, S.: Am. J. Path. 7: 105, 1931.

224. Dissman, E.: (Cited by Gross²²⁵).*Endocardial Sclerosis*

225. Gross, Paul: Arch. Path. 31: 163, 1941.

Defects of Interauricular and Interventricular Septa

226. Scammon, R. E., and Norris, E. H.: Anat. Rec. 15: 165, 1918-1919.

227. Patten, B. M.: Am. J. Path. 14: 135, 1938.
 228. Barnard, W. G.: Quart. J. Med. 23: 305, 1929-1930.
 229. Roger, H.: Bull. Acad. de méd. 8: 1074, 1879.
 230. Mall, F. P.: Anat. Rec. 6: 291, 1912.
 231. Cannell, D. E.: Am. J. Path. 6: 477, 1930.

Truncus Arteriosus

232. Abbott, M. E., and Shanly, E.: Internat. A. M. Museums Bull. 8: 188, 1922.
 233. Humphreys, Eleanor M.: Arch. Path. 14: 671, 1932.

Transposition of Great Vessels

234. Spitzer, A.: Virchows Arch. f. path. Anat. 248: 81, 1923.
 235. Harris, J. S., and Farber, S.: Arch. Path. 28: 427, 1939.

Pulmonary Stenosis and Atresia

236. Fallot, A.: Marseille méd. 25: 77, 138, 207, 270, and 403, 1888.
 237. Garrison, R. E., and Feldt, R. H.: Am. Heart J. 24: 685, 1942.
 238. Blalock, A., and Taussig, H. B.: J. A. M. A. 128: 189, 1945.
 239. Eisenmenger, V.: Ztschr. f. klin. Med. (Suppl.) 32: 1, 1897.

*Anomalies of Chordae and Endocardium**Chiari's Network*

240. Chiari, H.: Beitr. z. path. Anat. u. z. allg. Path. 22: 1, 1897.
 241. Helwig, F. C.: Am. J. Path. 8: 73, 1932.
 242. Yater, W. M.: Am. Heart J. 11: 542, 1936.

Fenestration of Semilunar Valves

243. Foxe, A. N.: Am. J. Path. 5: 179, 1929.

Subaortic Stenosis

244. Walsh, B. J., Connerty, Harold V. and White, P. D.: Am. Heart J. 25: 837, 1943.

Bicuspid Aortic Valves

245. Koletsky, S.: Arch. Int. Med. 67: 129, 1941.
 246. Koletsky, S.: Arch. Int. Med. 67: 157, 1941.
 247. Lewis, T., and Grant, R. T.: Heart 10: 21, 1923.

Patent Ductus Arteriosus

248. Christie, Amos: Am. J. Dis. Child. 40: 323, 1930.
 249. Gross, R. E.: J. A. M. A. 115: 1257, 1940.
 250. Bullock, L. T., Jones, J. C., and Dolley, F. S.: J. Pediat. 15: 786, 1939.
 251. Eppinger, E. C., and Burwell, C. S.: J. A. M. A. 115: 1262, 1940.
 252. Keys, A., and Shapiro, M. J.: Am. Heart J. 25: 158, 1943.

Anomalies of Coronary Arteries

253. Gross, Louis: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber, Inc.
 254. Smith, J. C.: Circulation 1: 1168, 1950.
 255. Soloff, L. A.: Am. Heart J. 24: 118, 1942.

Cyanosis

256. Lundsgaard, C., and Van Slyke, D. D.: Medicine 2: 1, 1923.

*The Pericardium**Anatomical Relations*

257. Kaufmann, E.: Pathology (Trans. by Reinmann), Vol. I, Philadelphia, 1929, P. Blakiston's Son & Co., p. 1.
 258. Burwell, C. S.: Diseases of the Pericardium, Oxford Medicine Vol. II, part 1, New York, 1940, Oxford University Press, pp. 251-284.

Congenital Anomalies

259. Southworth, H., and Stevenson, C. S.: Arch. Int. Med. 61: 223, 1938.

260. Cushing, E. H.: Arch. Int. Med. 59: 56, 1937.

Tamponade

261. Cohnheim, J.: Cited by Burwell.²⁵⁵

Cholesterol Pericarditis

262. Merrill, A. J.: Am. Heart J. **16**: 505, 1938.
 263. Daniel, G. and Puder, S.: Virchows Arch. f. path. Anat. **284**: 853, 1932.

Rheumatic Pericarditis

264. Bland, E. F., and Jones, T. D.: Arch. Int. Med. **61**: 161, 1938.

Tuberculous Pericarditis

265. Keefer, C. S.: Ann. Int. Med. **10**: 1085, 1936-1937.
 266. Harvey, A. M., and Whitehill, M. R.: Medicine **16**: 45, 1937.
 267. Rich, A. R.: Pathogenesis of Tuberculosis, Baltimore, 1944, Charles C Thomas.

Actinomycotic Pericarditis

268. Cornell, A., and Shookhoff, H. B.: Arch. Int. Med. **74**: 11, 1944.

Constrictive Pericarditis

269. Pick, F.: Ztschr. f. klin. med. **29**: 385, 1896.
 (Translated in part by P. D. White, in Heart Disease, ed. 3, New York, 1944, The Macmillan Co., p. 658.)
 270. Burwell, C., and Blalock, A.: J. A. M. A. **110**: 265, 1938.
 271. Paul, Oglesby: American Heart Association, New York **19**: 83, 1950.
 272. Harrison, M. B., and White, P. D.: Ann. Int. Med. **17**: 790, 1942.
 273. Beck, C. S.: Footnote in White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Co., p. 666.

Trauma to Pericardium

274. Bright, E. F., and Beck, C. S.: Am. Heart J. **10**: 293, 1934-1935.
 275. Crynes, S. F., and Hunter, W. C.: Arch. Int. Med. **64**: 719, 1939.

Tumors of the Pericardium

276. Yater, W. M.: Arch. Int. Med. **48**: 627, 1931.

Chapter 20

THE BLOOD AND LYMPHATIC VESSELS

ERNEST M. HALL

DISEASES OF ARTERIES

Anatomy and Physiology

The larger conducting arteries that carry blood away from the heart are of the elastic type. Included in this group are the aorta, innominate, subclavian, the first portion of the common carotid, and the pulmonary arteries. The *distributing arteries* composing the link between the elastic arteries and the arterioles are of the *muscular type*. These include the brachials, femorals, mesenterics, renals, hepatic, coronaries, etc. The smallest arteries, the *arterioles*, are only 0.3 mm. in diameter or smaller, just visible to the naked eye. Both muscular and elastic arteries are capable of considerable stretching, the latter more, of course, than the former, both returning to normal size passively, after being stretched.¹

Elastic Arteries.—The elastic arteries are large-caliber vessels nearest the heart where they are subjected to great rhythmically changing pressures as the heart contracts and relaxes. These are characterized by increased amounts of elastic tissue in the media. The tunica interna or intima is composed of endothelium, and a special subendothelial layer consisting mainly of a feltwork of elastic fibers arranged longitudinally which merges in to the *internal elastic membrane*. The latter is a dense sheet of fenestrated elastic tissue. The tunica medialis, the widest of the three layers, is formed mainly of elastic tissue with some collagenic fibers and muscle. The outer margin is fortified by a special concentration of elastic fibers, the *external elastic membrane*. The tunica adventitia is a relatively thin, poorly defined layer, composed chiefly of collagen, some elastic fibers, blood vessels, lymphatics and nerve fibers.²

Muscular Arteries.—A gradual transition exists between the larger elastic arteries and the smaller ones of muscular type characterized by replacement of elastic and collagenic fibers by muscle. The transitional arteries are of mixed type. These vessels are more directly under the control of the nervous system by virtue of their greater proportion of muscle. They are more abundantly supplied by nerve fibers and blood vessels than are the elastic arteries, and are, therefore, more responsive and less mechanical in their activities.²

Arterioles.—Arterioles are much smaller, but in structure resemble closely the muscular arteries. The lumen is small as compared to the thickness of the wall, usually in the ratio of about 1:2.² These vessels are like switches in a railroad yard which open or close under the hand of the tower man, thus controlling the flow of traffic. The arterioles to the various

organs dilate or constrict under the control of the autonomic nervous system, thus producing hyperemia or relative ischemia as function of the organ demands.

Systemic Arteries.—The coronary arteries are discussed in Chapter 19, page 476.

The cerebral arteries are peculiar in possessing thin walls due to poorly developed muscular coats with only one elastic lamina. The media is often extra-thin at the angle where a branch arises. Furthermore, the delicate pia-arachnoid provides scanty support for these vessels.

Capillaries.—Zweifach and associates^{3, 4} have studied the capillaries in the mesentery of the rat and dog as regards structure and function. The structural unit according to these authors consists of the prolongation of a terminal arteriole designated variously as a central or thoroughfare channel, arteriovenous capillary, or metarteriole (Gr. *meta*, beyond), together with its true capillaries which are given off abruptly along its course. Smooth muscle from the wall of the metarteriole continues on to the capillaries for a short distance. Zweifach calls these precapillary sphincters. Because of the sphincter-like action at the proximal ends of the capillaries, they are able to open or close in response to stimuli. The true capillaries consist of a single layer of endothelial cells (except for the precapillary sphincter) and average about 8 microns in diameter. No actual stomata or preformed openings are believed to exist in the walls of the capillaries.

Veins.—Veins have the same general structure as their accompanying arteries. Their caliber is greater, the blood pressure is lower, and the amount of muscle and elastic tissue is less. Some hours after death, the arteries are empty while the veins are filled with blood. This is apparently due to muscular contraction as rigor mortis sets in. It led the early anatomists to believe that the arteries conducted air, hence the term *artery*, meaning "air tube." Except for the inferior vena cava, most of the larger veins contain valves. These facilitate the movement of blood toward the heart by preventing retrograde flow.

The blood vessels are supplied by *efferent autonomic fibers*—both vasoconstrictor and vasodilator. The arterioles are particularly well supplied with such fibers. By stimulation of the vasoconstrictors the blood supply may be greatly reduced to a given organ. Excitation of vasodilators has the opposite effect; thus, for example, the blood is abundantly supplied to viscera during digestion and to the muscles during exercise. The brain is relatively ischemic during digestion but is well supplied with blood during exercise.

Congenital Anomalies

Hypoplasia of the aorta and larger arteries usually accompanies cardiac hypoplasia. The caliber of the larger vessels is smaller than normal and the walls are thinner. The condition may be seen in primary anemias and in *status lymphaticus*. Cerebral hemorrhage in young persons is often associated with a *status lymphaticus* constitution.⁵ Congenital hypoplasia of the ascending aorta occurred 77 times in Abbott's series⁶ of 1,000 congenital hearts. In only two instances, however, was this the primary lesion.



Fig. 393.—Double aortic arch viewed from above. The large aorta bifurcates to surround trachea and esophagus (central opening). The arteries coming off double arch are (left to right) right subclavian, right common carotid, left common carotid, and left subclavian.

Anomalies of the Aortic Arch.—The major anomalies may be divided into five groups which are listed approximately in the order of frequency⁷: 1. Coarctation of the aorta; 2. Patent ductus arteriosus; 3. Posterior right subclavian artery; 4. Right-sided aortic arch; and 5. Double aortic arch. (Fig. 393.)

Coarctation of the Aorta.—Two types of coarctation are recognized, viz., (a) the infantile type, which is usually fatal within a few days or weeks after birth, and (b) the adult type.

The *infantile type* of coarctation is quite variable and is usually accompanied by other grave anomalies. The fundamental abnormality is a diffuse narrowing of the isthmus which lies between the left subclavian artery and the point of entrance of the ductus arteriosus.⁸ Frequently the entire arch of the aorta is hypoplastic and

the ductus is usually of large caliber (Fig. 394). Because of the large ductus collateral circulation is not developed.

In the *adult type* the mean age in the cases analyzed by Abbott⁸ was 33 years. Because of the characteristic symptom complex, much has been written on this anomaly.⁹ The principal lesion is a constriction or complete closure of the aorta immediately beyond the attachment of the ligamentum arteriosum. Increased intra-aortic pressures in the aortic arch (hypertension) result in cardiac hypertrophy. The aortic arch dilates in about half of the cases and occasionally ruptures due to the increased pressure. Abbott⁹ has analyzed about 200 cases of the adult type that have come to autopsy. Of this group 47 had complete atresia, 108 extreme, and 45 moderate stenosis of the descending arch of the aorta near the insertion of the ductus arteriosus. Survival is possible in patients who develop an adequate collateral circulation. Those who reach adulthood develop extremely large, complex anastomoses. The internal mammarys, vertebrals, superior intercostals, transverse cervical, and inferior thyroid arteries are as a rule tremendously dilated, while many smaller, less important vessels are likewise affected. Occasionally, the right aortic arch persists to become a dilated collateral vessel.¹⁰ By means of these circuitous channels the blood in the aortic arch is conducted past the point of obstruction and much of it eventually returns to the aorta (Fig. 395). Under these circumstances, the blood pressure is considerably reduced in the lower extremities. Due to the enlarged intercostal vessels, pulsations can be felt over the back and not infrequently



Fig. 394.—Coarctation of the aorta, infantile type. Female infant who lived only 3 days. Note hypoplastic aortic arch, huge pulmonary truncus with large ductus arteriosus. Other anomalies— aortic valvular stenosis, atrioventricular septal defects.

seen in the supraclavicular spaces. Notching of the undersurfaces of the ribs as seen in the roentgenogram is diagnostic of the disease. Of the 200 cases studied by Abbott,⁹ cardiac failure was the greatest cause of death (33.5 per cent). Other causes were dissecting aneurysm, rupture of aorta or heart, cerebral softening or hemorrhage, and mycotic endarteritis.

Arteriosclerosis

Arteriosclerosis is the keystone in the arch of cardiovascular disease. Our knowledge of the etiology of this disease is still fragmentary notwithstanding its great importance. Until the causes are known prevention will necessarily remain on an empirical basis. At the present time many outstanding clinicians and

the larger conducting arteries consisting of fibrous and lipoid-containing plaques, arteriosclerosis includes, as well, medial calcification of Mönckeberg, and arteriolar sclerosis. The latter includes degenerative and proliferative changes which occur in the peripheral arterioles usually associated with hypertension.

Marchand, in 1904, coined the term *atherosclerosis* (Gr. *athere* = mush), to designate the lipoidal degenerative and sclerotic changes in the arteries. Although it has been objected to by eminent authorities, the term is becoming well established. It is convenient in designating the atheromatous type of arteriosclerosis.

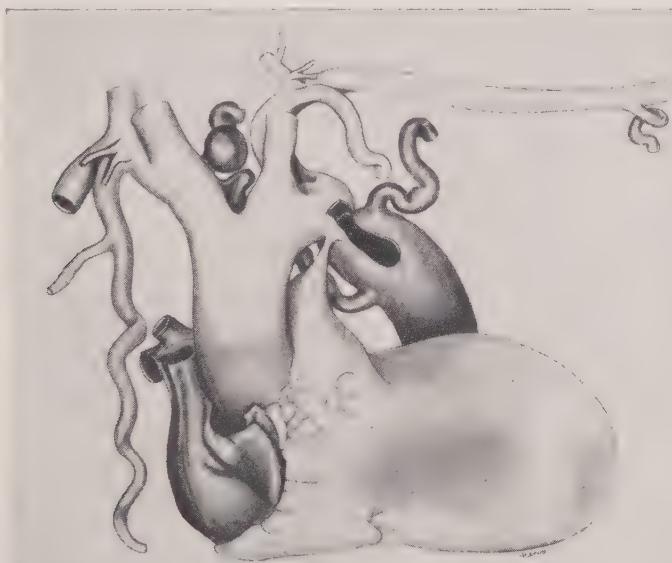


Fig. 395.—Coarctation of aorta, adult type. Drawing of a specimen obtained from the anatomical laboratory. The heart is large, with dilated aorta. A window has been cut in the constricted part. The ductus, which is closed, seems to produce some tension on the constricted area. Note the dilated arteries constituting part of the anastomotic system of vessels.

basic scientists in medicine and related fields are attacking this problem from every possible angle. Flickers of light are beginning to dawn and, no doubt, much important knowledge will be forthcoming within the next decade or two.

Arteriosclerosis means, literally, "hardening of the arteries" (Gr. *skleros* = hard). The term is used to cover a variety of anatomical lesions produced no doubt by a number of different agents. Besides the common degenerative and proliferative changes in the intima of

THE ANATOMICAL LESIONS

Atherosclerosis.—Atherosclerosis, the most common alteration of arteriosclerosis, consists of intimal fibrosis and lipoidosis. It is agreed that the primary change is in the intima, but precisely what the initial change is has not been established. Splitting of elastic fibrils is observed in the deeper parts of the intima accompanied by destruction of some of the connective tissue. At the same time fat droplets appear usually in the

depths of the intima (Fig. 396). These consist of neutral fats, often crystalline plates of cholesterol and doubly refractive masses of cholesterol esters.^{11, 12} Nile blue sulfate stains indicate the presence of some fatty acids. Concurrently with accumulation of lipoids in the depths of

cap appear gray, while those with thinner covers of fibrous tissue are yellowish. In elderly persons the plaques may be thinly covered and easily ruptured. When this happens in the aorta during an autopsy, the granular, yellow-colored pultaceous material may be observed to well up to the depth of a centimeter or more (Fig. 397). In younger persons, on the other hand, the plaques are often firmer and rupture is less frequent. Calcification is often a conspicuous part of the atheromatous process. It tends to occur in the fibrous tissue bordering the lipoid accumulations (Fig. 398). It may be present in the hyaline fibrous tissue cap. At times it forms a thin eggshell layer in the intima, cracking into thin plates on handling.

Medial Calcification (Senile Arteriosclerosis or Mönckeberg's Sclerosis).—Medial calcification is a process quite different from atherosclerosis. It affects the muscular arteries such as the femorals, tibials, radials, and temporals. The etiology is probably dependent upon vaso-tonic influences acting through the sympathetic nervous system on the wall of the vessel itself. These causes would appear to be quite foreign to those causing atherosclerosis. On the other hand, Blumenthal and his associates¹³ describe a diffuse, finely dispersed calcification of the aortic media, dependent primarily

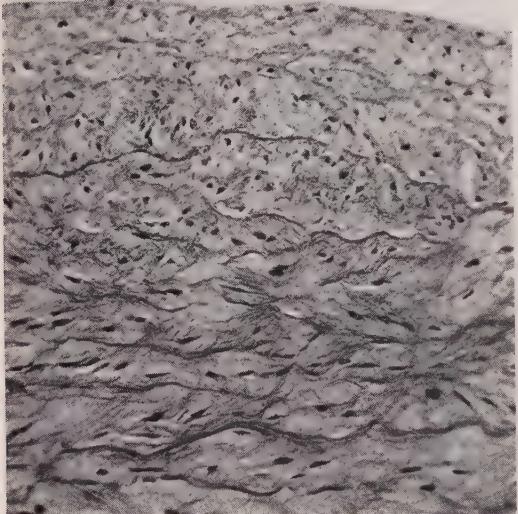


Fig. 396.—Early atherosclerosis. Note the pale loose connective tissue of the intima with fraying of the internal elastic membrane. The small clear spaces about the cell nuclei are due to lipoids which have been dissolved out of the macrophages in preparing the section.



Fig. 397.—Senile atherosclerosis. (Note the numerous raised atheromatous plaques. These are soft and easily ruptured, leaving atheromatous ulcers. White man, aged 78 years.)

the intima, connective tissue proliferation occurs near the inner surface. Thus, as the lipoids form atheromata, the covering becomes thickened, often consisting of dense hyaline fibrous tissue. The color of the plaques in the aorta varies according to the relative amounts of lipoid and fibrous tissue—those with a thick fibrous

upon age. In the Mönckeberg type the early alterations probably consist of degenerative changes in the muscularis, namely, hyaline and fatty degeneration followed by necrosis. Calcium is deposited in the form of plaques in the mid-portion of the media (Fig. 399). When a large artery such as the femoral is in-



Fig. 398.—Section through an advanced atheromatous plaque. Numerous cholesterol clefts are seen in the pale central part. The small dark spots are due to calcium deposits.

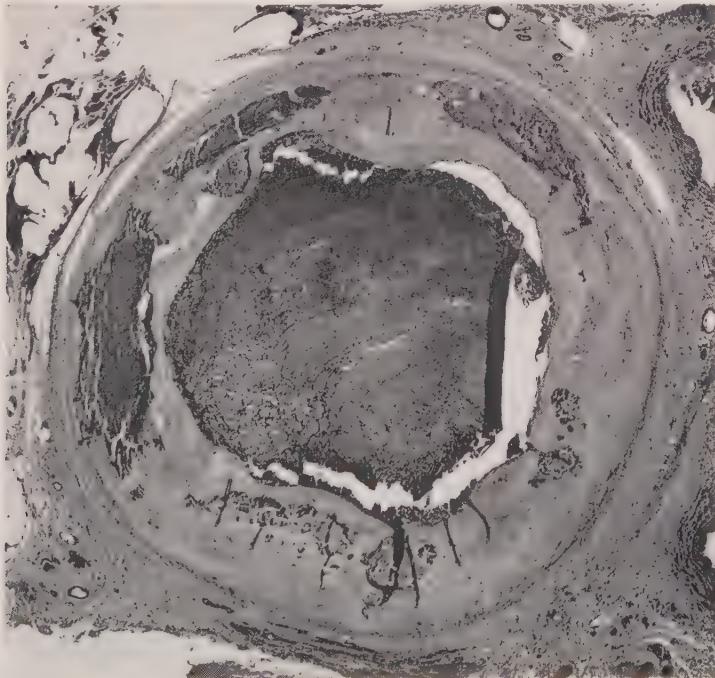


Fig. 399.—Mönckeberg's medial sclerosis. Note the dark calcified plaques in the media. A recent thrombus fills the lumen.

volved, the inner wall has a "corduroy" or "gooseneck" appearance due to the broken rings of calcium. Smaller arteries, such as the radials, exhibiting

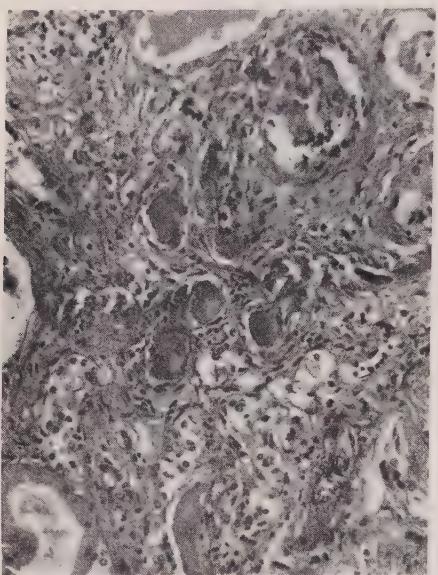


Fig. 400.—Necrotizing arteriolitis in malignant nephrosclerosis. The arterioles appear as dark smudges.

these changes are the so-called "pipe-stem" arteries. Similar lesions have been produced experimentally in dogs and rabbits by injecting large doses of epinephrine to induce prolonged spasm of the vessels.^{14, 15} Other vasotonic agents that act similarly are nicotine, parathyroid hormone, and vitamin D.¹⁹ Medial calcification is often combined with intimal atheromatous lesions in the same artery. The coronary arteries may be affected to some degree by medial deposits of calcium but atheromatous-plaque formation is the most conspicuous change. Medial calcification is a degenerative change manifest in muscular arteries due to toxic vasotonic agents of exogenous or endogenous origin, according to the view of Hueper.¹⁷ It is one phase of the arteriosclerotic process.

Arteriolosclerosis (Arteriolar Sclerosis).—Arteriolosclerosis, as the term indicates, refers to changes in the small peripheral arteries. These changes consist of various types of hyperplastic thickening of the vessels with consequent

narrowing of the lumina. Although the etiology is not established, it appears to be related to increased intravascular pressures and vasospastic influences. The lesions are anatomically and etiologically different from those of atherosclerosis. The arteries affected are those that respond most actively to nervous influences and those that regulate the blood supply to the important viscera. Several histologic types are described: (a) intimal hyalinization, (b) medial hypertrophy, and (c) endothelial hyperplasia.¹⁸ The *hyaline* type with subintimal deposition of hyaline material is the most common. Longitudinal sections show that this material is deposited along the vessel wall in masses of unequal thickness. The lumen of the vessel is reduced in size and contractility of the muscular wall is lessened. These changes are observed most frequently in arteries of the spleen, kidney, pancreas, and liver (Fig. 447). They are rarely found in the skin and intestinal tract.¹⁹ Severe degrees of hyaline thickening are seldom present except in association with hypertension. The renal arterioles in severe grades of hypertension often exhibit fibrous intimal thickening. In malignant hypertension "necrotizing arteriolitis" may affect the afferent glomerular vessels and their extensions. In hematoxylin-eosin stained sections these lesions appear as hyaline, smudgy rings (Fig. 400). The necrotic change is almost universally associated with azotemia and



Fig. 401.—Elastic tissue hyperplasia in malignant nephrosclerosis.

is believed to be the result of the elevated nonprotein nitrogenous waste materials in the blood. *Medial hypertrophy* together with degeneration of collagen is seen most frequently in the skeletal muscles in chronic hypertension. There appears to be no preference for any muscle group except that the diaphragm tends to be spared.¹⁸ In medial hypertrophy the smooth muscle fibers are large and their nuclei are prominent. The wall is thickened, usually without thickening of the intima. If degeneration of collagen is present, the muscle fibers are largely replaced by fibrous tissue and the wall appears less thick. In *endothelial hyperplasia* the intima is thickened usually by proliferation of fibroblasts and subsequent laying down of collagen. The new tissue varies considerably in the number of nuclei present. This type of noninflammatory proliferation occurs most frequently in renal vessels over 30 microns in diameter. The internal elastic membrane appears intact in this group marking the junction of intima and media. In somewhat larger renal arteries the intimal thickening may be associated with proliferation and reduplication of the internal elastic membrane¹⁸ (Fig. 401).

EXPERIMENTAL ARTERIOSCLEROSIS

A great number of investigators have devoted their time and energy to the matter of producing arterial lesions experimentally. In these efforts various substances have been tried, including vasotonic and toxic agents, bacteria and bacterial toxins, physical and mechanical factors, and a good many dietary regimens. Of the latter, cholesterol has been tried most often and has produced fairly striking results in the rabbit, dog, and chicken. Of the animals tested, the rabbit has been the most responsive.

Adrenalin-type Scleroses of Arteries.—The studies of Josue²⁰ (1903) demonstrated the possibility of producing medial calcification in the arteries of the rabbit by injections of adrenalin. Other vasotonic substances that act similarly are nicotine,²¹ ergotine,²² and angiotonin.²³ Hueper²² believes the result comes about because of spasm of the vessels. Prolonged spasm causes anoxemia of the muscular coat, followed by degeneration, necrosis, and finally calcification. Toxic substances, such as diphtheria toxin, produce medial necrosis probably through direct toxic action on the muscle followed by calcification. Klotz²⁴ pointed out that the nature of the ground substance and the presence of phosphatase are the factors which determine the deposition of calcium salts in cartilage and bone.

Effect of Bacteria and Their Toxins.—The presence of toxins of bacterial origin supposedly

exerts specific cytotoxic effects upon the vascular wall, thereby producing various types of degenerative arterial lesions.^{17, 25} Despite investigations in which bacterial toxins or other bacterial products were injected into experimental animals, the results have been generally disappointing.^{26, 27}

Atherosclerosis Resulting from Dietary Factors.—A great many attempts have been made in recent years to produce atherosclerosis in laboratory animals by the feeding of fats, lipids, cholesterol, or proteins. The animal most frequently used, the rabbit, has been fed diets entirely foreign to his natural appetite. The quantities have also been excessive when the size and weight of the animals are considered.

The first feeding experiments of importance that produced arterial lesions were those of Ignatowski²⁸ (1908). He induced nodular intimal lesions in the aortas of rabbits by feeding meat, milk, and eggs. These early experiments probably led Anitschkow^{29, 30} to embark on his classical work. He demonstrated that dependable results could be obtained in the rabbit by feeding pure cholesterol dissolved in vegetable oil. The effect of such feeding was the production of hypercholesterolemia with subsequent precipitation of cholesterol esters from the blood into various organs including the arteries. Such increase in the concentration of cholesterol in the blood produces a xanthoma-cell response in many organs. Alterations are seen as well in the intercellular substance. Wacker and Hueck,³¹ McMeans and Klotz,³² and others have all obtained results comparable with those of Anitschkow in cholesterol feeding of rabbits. It is interesting that the feeding of small doses of cholesterol (below 150 mg. daily) over long periods gave negative results. It must be kept in mind that the rabbit is herbivorous and not accustomed naturally to high concentrations of cholesterol in the diet. Similar feeding experiments using dogs and cats (carnivora), rats and mice (omnivora) were negative at first.

Steiner and associates³³ have produced experimental atherosclerosis in dogs by feeding cholesterol plus thiouracil. Results obtained with carnivorous animals such as the dog more closely reproduce the lesions seen in man than do those reported in the rabbit. It was necessary, however, to maintain the serum cholesterol level above 450 mg. per cent for more than 12 months to produce atherosclerotic lesions in dogs.

Pathologic Anatomy of Arterial Lesions Produced by Cholesterol Feeding.—Anitschkow²⁹ described yellow streaks or round yellow patches in the intima of the first half of the aorta. Later these areas may become warty or button-like but are confined mainly to the thoracic aorta. Plaques may appear also in the coronary, pulmonary, renal, mesenteric, splenic, and iliac arteries. The lesions persist for weeks or months after cholesterol feeding is discontinued but gradually the lipid is absorbed and the plaques disappear. No advanced arteriosclerotic lesions have been produced in the rabbit.

Microscopically, one sees an early deposit of fat granules in the interstitial substance of the

intima lying between the endothelial cells and the elastic layer (Anitschkow). The ground substance into which the lipoid is deposited has increased in quantity and has become hyaline-mucoid in character. Klotz³⁴ believed that this change precedes the lipoid deposit and constitutes the chief factor which determines the laying down of lipoid substance in this layer.

Duff³⁴ has objected to the results obtained in the rabbit on the grounds that the distribution of the lesions was not comparable to that in man. In the human being the abdominal aorta and the cerebral arteries are severely involved while in the rabbit these areas, as well as the renal arteries, are spared. Furthermore, only the early stages of atherosclerosis can be produced in the rabbit. Duff further criticized the experiments because they failed in the carnivora such as the dog, cat, fox, etc. Since the successful results with cholesterol and thiouracil feeding in the dog, Duff's objections have largely been met. The distribution of lesions in the dog is similar to that in man. In addition, advanced lesions occur with lipid and cholesterol deposits, fibrous tissue proliferation and calcification. These results come much nearer to reproducing the lesions in man than do those obtained in the rabbit.

THEORIES ON THE ETIOLOGY OF ARTERIOSCLEROSIS

The Relations of Arteriosclerosis to Senescence.—Are the degenerative and sclerosing changes observed in the arteries, in general the results of the aging process, modified perhaps by other factors? Arteriosclerosis becomes more common after 40 and is the principal cause of death after 65 years of age.³⁵ Together with hypertension it causes 25 per cent of deaths after 65 years.³⁶ Although arteriosclerosis becomes increasingly manifest in older individuals up to 75 to 80 years, it is not directly the result of aging. Atheromatous changes are seen relatively frequently in the coronary arteries and the splenic arteries of young adults at a period when the aorta exhibits considerable elasticity. White and associates³⁷ reported that the degree of coronary sclerosis in necropsy material is not linearly related to age. It increases rapidly in the 30- to 49-year period, reaches a maximum in the 50- to 59-year group and thereafter remains at a fairly constant level. A progressive loss in extensile and retractile properties of the aorta continues throughout adult life at a fairly uniform rate for a given part of the vessel. All persons appear to be affected about equally, regardless of intimal atheromatosis.³⁸ According to Hass,³⁹ the elastic tissue of the arteries undergoes "axial crystallization" beginning in the fourth to fifth decade, and, later, granular disintegration occurs with partial fibrous tissue replacement accompanied by reduction in tensile strength. These changes lead to *senile ectasia* and to elongation and tortuosity of the conducting arteries. These are changes due to aging tissues but are not specifically those of arteriosclerosis. Wilens³⁸ observed loss of the wavy character of elastic fibrils with increasing age and failure to recoil to any effective degree on relaxation.

Fine diffuse calcification of the aortic media was found by Blumenthal and associates⁴⁰ to be correlated with age. In the muscular arteries, splitting of the internal elastic membrane is observed beginning in youth and gradually becoming more complete with increasing age. New elastic tissue membranes may form while new connective tissue is laid down in the spaces between these layers.³⁵ Thus, with age, although the vessel dilates and becomes more tortuous, at the same time the wall thickens. The lesions of arteriosclerosis are distinctly spotty, while changes in the arteries due to senility are usually diffuse.

Mechanical Trauma.—Since hemodynamic forces are constantly acting on the arterial walls, it is natural to ascribe to these forces effects resulting in, or predisposing to, arteriosclerosis. Such forces as tension, vibration, and shearing are described as effective in loosening connective tissue ground substance or in separation of intima and media, thus favoring imbibition of lipid-containing plasma and stimulating intimal proliferation. Mechanical factors are believed to be operative in the localization of plaques on the aorta along its posterior wall where it is more or less fixed to the spinal column by the segmental arteries.⁴⁰ A similar situation exists with the internal carotid arteries as they pass through the base of the skull. Arteries associated with moving parts such as the joints and muscles exhibit less arteriosclerosis than do fixed portions of the same vessel. It is believed that movement and massage by muscles improves nutrition of arterial walls, thus preventing arteriosclerosis.⁴¹ High intravascular pressure present in the arteries is, no doubt, an important factor in localizing atheromatous plaques in these vessels. Low blood pressure tends to decrease while hypertension tends to increase the amount of arteriosclerosis. Hueper⁴² supports the idea that eddies and currents are greater at anatomical points of stress and that instability of the plasma colloids would, therefore, tend to cause their precipitation at such points. Dock⁴³ aptly refers to this as a "churning effect."

Virchow-Aschoff Imbibition Theory.—In 1856 Virchow⁴⁴ stated that the first changes in the production of arteriosclerosis consisted in "a certain loosening of the connective tissue ground substance" of the intima. This he "attributed in large measure to an increased imbibition of fluid elements from the passing blood stream." Along with widening of the connective tissue spaces observed microscopically, there was proliferation of the connective tissue to form local thickenings of the wall. Aschoff⁴⁵ accepted the idea of imbibition of fluid from the blood but ascribed the changes in the intercellular ground substance to colloidal aging.

Theory of Leary.—Leary⁴⁶ believes that "atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells which first appear in the intima of the arterial wall."

Theory of Winternitz, et al.—Winternitz and associates⁴⁷ studied normal arteries in areas of inflammation. They demonstrated greater vascularity of the vessel wall than was previously suspected. This change was especially marked

when vascular disease was present. Besides the usual nutrient arteries arising in the adventitia and distributed through the media, many capillaries were demonstrated opening into the lumen of the vessel. Since hemorrhage occurs near sites of predilection of atherosclerosis, it is assumed that vascularitis, hemorrhage, and sclerosis are related. Winternitz and associates⁴⁷ believe hemorrhages and exudations into the vascular wall are contributing sources for the production of atheroma. It is suggested in criticism of this idea that intimal vascularization, exudation, and hemorrhage may be secondary to arteriosclerosis rather than primary.

Anoxemia as a Factor in the Production of Vascular Lesions.—Hueper,⁴⁸ in a comprehensive recent review of the subject of arteriosclerosis, outlines a new concept called the "Theory of Anoxemia." It is applicable to all the various anatomical types of arteriosclerosis. Anoxia is seemingly produced by a great variety of chemical and physical agents, both endogenous and exogenous. A fundamental mechanism is proposed by Hueper through which the various kinds of causal agents and their different causal mechanisms affect the vascular walls, that is, by interference with the "oxidative metabolism and nutrition of the vascular wall." Hueper⁴⁸ thus introduces a mechanism of basic importance supported by considerable experimental data and many well-known observations.

Page⁴⁹ suggests that two factors assist in the production of human atherosclerosis. One is lipemia, which appears to be important in diabetes, nephrosis, and xanthomatosis. The other factor or factors are presumably related to hypertension, since hypertension alone may induce atherosclerosis without hyperlipemia.

The Relation of Atherosclerosis to Lipid Metabolism.—The relation of blood lipids to human atherosclerosis is controversial. Some observers have reported increases in blood lipids in atherosclerosis while others have not. The problem is difficult to study directly since the diagnosis of atherosclerosis in the living subject must be made largely by inference. It is assumed, for example, that patients suffering from angina pectoris, myocardial infarct, or senile gangrene of the extremities have atherosclerosis. Recent studies are based chiefly on the presence of acute myocardial infarction. Although in the past it has been held⁵⁰ that many, if not most, instances of atherosclerosis are unaccompanied by hypercholesterolemia, there is evidence, more recently, that in the majority of instances myocardial infarction occurs in the presence of elevated plasma cholesterol. This has been reported by Steiner and Domanski⁵¹ who studied 15 patients with coronary sclerosis over periods of 2 to 26 months. The average cholesterol level in this group was 355 mg. per 100 c.c. of serum. The average cholesterol level in 15 control patients studied for 12 months was 255 mg. per 100 c.c. of serum, an average increase of 100 mg. Morrison and associates⁵² obtained somewhat similar results with a much larger number of patients. It is proposed also that not only are the blood levels of cholesterol elevated in coronary atherosclerosis but the serum cholesterol tends to fluctuate widely in contrast to a rela-

tively constant level in the normal person.⁵³ Gertler and associates⁵³ reported a study in agreement with both of the above ideas and add that serum phospholipids are highly correlated with serum cholesterol. They hypothesize that the ratio of cholesterol to phospholipids is more important than the actual levels of these substances in the serum.



Fig. 402.—Atheromatous plaques of the aorta localized about the openings of the intercostal arteries. White man, aged 23 years.

In experimental atherosclerosis various species exhibit inability to keep serum phospholipids on a level with serum cholesterol when high cholesterol feeding is in progress. Davidson and associates⁵⁴ have shown that a cholesterol phospholipid molar ratio of 1:1 in normal dogs may go to 5:1 in cholesterol-thiouracil fed dogs in which atherosclerosis has been produced.

On the other hand, it has been shown that certain substances are capable of decreasing the incidence and severity of experimental atherosclerosis in cholesterol-fed rabbits. Serum phospholipids as well as serum cholesterol are markedly elevated in these animals. It is suggested that serum phospholipids exert a stabilizing effect upon the colloid state of cholesterol in the blood. Lecithin, the chief phospholipid of serum, is a well-known emulsifying agent. Kellner and associates⁵⁵ have demonstrated that

certain detergents such as Tween 80 and Triton A-20 injected intravenously into rabbits on a high cholesterol diet retarded or prevented the development of atherosclerosis.

The recent work of Gofman and associates⁵⁶ relating serum lipids to atherosclerosis has attracted widespread attention. (See page 478.) Utilizing the analytical ultracentrifuge and a flotation technique Gofman has been able to separate from serum a number of "giant molecule" lipoprotein complexes of different densities. One group, designated the S_r 10-20 class, is found in much higher concentrations in the group of patients with myocardial infarction than in the normal controls. This suggests a relationship between the large aggregates of lipoproteins of this particular density and atherosclerosis. Further evidence of this relationship is seen in experimentally produced atherosclerosis in rabbits. While the S_r 10-20 molecules are not increased in the normal rabbit, they eventually appear in high concentration in the atherosclerotic animal. Lewis and Page⁵⁷ have confirmed the results of Gofman and associates.

Although the concentration of S_r 10-20 molecules bears no direct relation to the total cholesterol level of the blood, there is a trend toward higher S_r 10-20 concentrations with high total cholesterol. It is encouraging that adherence to a diet restricting cholesterol to 200 mg. or less and fat to 50 Gm. or less, daily for periods of a month or longer, results in consistent lowering of the concentration of these molecules.

While Turner and Steiner⁵⁸ and Keyes⁵⁹ have shown that addition of considerable amounts of cholesterol to the diet have not resulted in raising the serum cholesterol level, yet if cholesterol is almost eliminated in a diet that is essentially fat free, a rapid decline in serum cholesterol usually occurs. Experiments suggest that fat is just as important as cholesterol in maintaining a high level of serum cholesterol.⁴⁸

White⁶⁰ found that diabetics with high plasma cholesterol levels were fifteen times as likely to develop atherosclerosis as diabetics with normal cholesterol levels. It seems evident that one factor in the production of atherosclerosis is lipemia, no doubt important in diabetes mellitus, nephrosis, myxedema, and xanthomatosis. Another factor, according to Page,⁴⁹ is the strain of prolonged hypertension acting upon the vessels themselves.

If hyperlipemia developed with increase in age, it would be logical to assume that the higher lipid content of the plasma predisposed to atherosclerosis. Page and associates⁶¹ found in persons ranging from 29 to 90 years no significant difference in the amount or composition of the plasma lipids. Hyperlipemia is, therefore, not a characteristic feature of old age. It seems important to know whether or not the lipid mixture deposited in the arterial walls is similar to that of the plasma. Analyses made by Weinhouse and Hirsch⁶² and by Page⁶¹ on human aortas demonstrate the lipids to be present in nearly the same proportions as in the plasma. These results are highly suggestive that lipids in the aorta are derived from the

plasma. Atherosclerosis experimentally produced in the rabbit by excessive amounts of cholesterol in the diet is not characterized by high cholesterol content alone but the lipid mixture is proportional to that in the plasma.⁴⁸

The oriental peoples such as the Chinese, Japanese, Okinawans, etc., who subsist on fat-poor and cholesterol-poor diets develop minimal atherosclerosis, as is shown at autopsy, while coronary sclerosis and myocardial infarction are practically unknown.^{63, 64, 65} In Finland arteriosclerosis caused only half as many deaths during the war years as compared to the pre-war period. During World War II there were shortages of meat, eggs, milk, butter and grains.⁶⁶ Contrary to the usual conception, the Eskimo lives on a high-protein, low-fat diet. He exhibits no increased tendency to develop vascular or renal disease. The Greenland Eskimo's diet consists of raw fish and raw or dried lean meat with some vegetables in the summer. Fat is conserved for light and fuel.⁶⁷

To quote Dock⁴³: "Today, over most of the earth, want is the rule, and atherosclerosis is being prevented by chill penury. Where a luxus diet prevails, diabetes and atherosclerosis flourish."

Heredity and Constitutional Factors in Relation to Arteriosclerosis.—The tendency for atherosclerosis, especially coronary sclerosis, to occur at younger ages in successive generations suggests that heredity is a factor.⁶⁸ Weitz⁶⁹ has approached the problem from the standpoint of hypertension since this condition is important in the production of atherosclerosis. He concludes, "Dominant inheritance (of the predisposition for hypertensive disease) seems to me in the majority of cases to be certain."

Endocrine factors are of some importance as evidenced by the sex difference in coronary sclerosis especially in younger persons. Myocardial infarction before 40 years of age is fairly common in men but rare in women. Paroxysmal hypertension in patients with adrenal medullary tumors, and hypertension in Cushing's disease show the effects of excess secretion of epinephrine. Likewise, hypertension is frequently observed following the menopause. Thyroid deficiency is a recognized accelerator of the atherosclerotic state.

SUMMARY OF ETIOLOGICAL FACTORS IN ARTERIOSCLEROSIS

The etiology of the various types of arteriosclerosis remains in doubt. Factors that seem to play some role in producing these conditions are:

1. Neurogenic factors are believed by many to be of great importance in the production of arteriosclerosis. Coronary sclerosis, especially, occurs predominantly in business executives, physicians and other professional men, and persons generally holding responsible positions where competition, stress, and strain are great. The incidence is much lower among farmers, laborers, and rural groups gen-

erally. Hypertension is commonest also in the same group in which coronary sclerosis is frequent.

2. Chemical analyses of the lipids in atheromatous plaques and of the lipids of the plasma show similar kinds and amounts in the two places, indicating that atheromatous deposits are derived from the plasma.

3. Injury to the arterial wall may be a factor which promotes deposition of lipids, calcium, etc. Such injuries may be mechanical (hypertension), chemical (toxic), or metabolic (anoxemia theory of Hueper). Nicotine and adrenalin are common hypertonic agents. These act on the muscular arteries and arterioles rather than on the larger vessels, tending to produce medial calcification and arteriosclerosis.

4. Diet is probably important since in conditions that tend to increase blood cholesterol there is an increased tendency to atherosclerosis, as in diabetes, myxedema, glomerulonephritis, and xanthomatosis. The native Chinese, Okinawans, etc., whose diet is low in animal products, have minimal atherosclerosis. The neurogenic factor is probably of little importance among these peoples because of their philosophical outlook on life and because of their reduced tempo of living.

5. Experimental cholesterol feeding of rabbits and dogs with the necessity of high cholesterol blood levels supports the above premise. Another factor, the relation of phospholipids to cholesterol levels, is also important. Phospholipids act as emulsifiers or detergents and when present in adequate amounts prevent the development of atherosclerosis, at least experimentally.

6. It has now been shown that cholesterol levels in the blood tend to be elevated in atherosclerosis, involving the coronary arteries. This is contrary to former concepts.

7. The work of Gofman and others has introduced a new concept in the etiology of atherosclerosis. In patients with coronary sclerosis high concentrations of large aggregates of lipoprotein molecules are found in the serum. These have a density S_f 10-20 on the Svedberg scale. Diets low in cholesterol and fat tend to lower the concentration of large molecules in the blood.

8. Senescence is accompanied by certain degenerative changes in the elastic arteries, such as deterioration of elastic tissue and consequent dilatation of the lumen due to stretching. These changes are usually accompanied by some proliferation of the subendothelial connective tissue. Atherosclerotic plaques are commonly found in such arteries but are not necessarily caused by the aging process. Young men in their twenties may have atherosclerotic aortas without evidence of senescence. (Fig. 402.)

Inflammatory Lesions of Arteries (Peripheral Vascular Diseases)

ACUTE ARTERITIS

This is a general term including, for the most part, secondary lesions in the arteries due to a variety of infectious processes. Abscesses and other localized infections in the tissues may involve the outer coats of an artery, producing an acute periarteritis. Such a vessel may become thrombosed or weakened to the point of rupture. Rupture causes hemorrhage, which when localized results in a hematoma or a false aneurysm. The blood may enter a body cavity or appear on the surface. Infection arises most often from within, commonly the result of septic embolism in cases of bacterial endocarditis. The intima and media are most frequently affected. Abscesses and mycotic aneurysms are produced in this way. Endarteritis of the aorta and pulmonary artery are due to direct extension of an infective process from the aortic or pulmonic valves. Congenital or healed sclerosing lesions predispose to acute infections of the arteries (Fig. 403).

GRANULOMATOUS LESIONS OF THE ARTERIES

Syphilis of the Arteries: Syphilitic Aortitis.—Next to rheumatic heart disease, syphilis is the commonest and most important infectious cardiovascular disease.⁷⁰ The disease is preventable and appears to be on the decline, at least in the larger medical centers. According to Clawson and Bell,⁷¹ it constitutes about 2.6 per cent of all cardiovascular disease. Among southern Negroes, on the other hand, it may reach 25 per cent.⁷⁰ The death rate is greatest in the fifth and sixth decades. Death was due to aortic

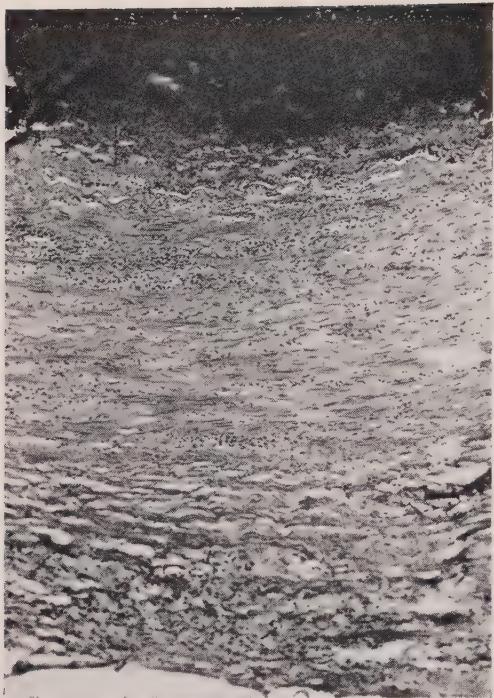


Fig. 403.—Acute thromboarteritis, popliteal, following comminuted fracture of both bones of leg just below the knee due to a crushing type of injury. Note numerous polymorphonuclear leukocytes infiltrating all coats of the vessel.

insufficiency in 36.5 per cent of the cases studied by Clawson and Bell.⁷¹ Nearly 5 males are infected for every female.

PATHOLOGIC ANATOMY.—Syphilitic aortitis belongs to the tertiary stage of the disease, manifesting symptoms on an average of twenty years after the chancre or primary infection. In congenital syphilis the aorta may be involved early, as in Lippman's⁷² patient, a youth of 17 years. The appearance of the lesion varies somewhat with the age of the patient, atheromatous changes tending to obscure the syphilitic process in the older age group.⁷³ In the classical example, wrinkling and fissuring of the intima are prominent, giving way here and there to depressed scars with radiating lines. These scarred areas give the impression of having been hammered out like brass or copper. Raised, smooth, fibrous plaques in the intima, in younger persons, are pearly, opalescent, or cartilaginous in appearance (Fig. 404). Eventually these may become atheromatous in character (Fig. 405). The aorta is usually thicker than normal, due largely to fibrous thickening of the adventitia. The process is usually confined to the arch of the aorta, seldom extending below the level of the diaphragm. Occasionally, patches



Fig. 404.

Fig. 404.—Syphilitic aortitis. Note raised smooth plaques and wrinkled depressed scars. White male, aged 53 years.



Fig. 405.

Fig. 405.—Atheromatosis associated with syphilitic aortitis. Negro male, aged 52 years.

of aortitis are present in the abdominal portion. Saphir and Scott claim that the first 4 cm. of the ascending aorta is more abundantly supplied with vasa vasorum than other parts of the aorta. Lesions of the aortic valve occur only when the first part of the aorta is heavily involved. When the aortic valve becomes involved, as it does in about 50 per cent of the cases, regurgitation and cardiac hypertrophy of the left ventricle follow as a result of shortening and thickening of the cusps with rolling of their edges and separation of the commissures (Figs. 404 and 405). The large elastic arteries arising from the arch of the aorta are frequently involved by the syphilitic process. The proximal ends of these vessels may be the site of a syphilitic mesarteritis with intimal proliferation resulting in stenosis. Aneurysm of the innominate artery is not uncommon. The syphilitic process is confined as a rule to the proximal few centimeters of these vessels.

The microscopic appearance of the aorta varies with the age of the lesion. The early changes consist of obliterative endarteritis of the vasa vasorum and perivascular infiltration in the adventitia with plasma cells and lymphocytes. The media may show myxomatous changes together with small areas of necrosis indicating a nutritional failure.⁷³ Older lesions reveal extensive necrosis of elastic tissue with granulation and fibrous tissue filling in the defects in the media. Round cells, mainly plasma cells and lymphocytes, infiltrate the scars and the adjacent media (Fig. 406). The process is very chronic, resulting in fibrous tissue replacement of much of the elastic tissue and muscle. The wall becomes distinctly weakened by this gradual destructive and proliferative process since the high grade musculo-elastic elements are constantly being exchanged for the inferior fibrous tissues. The result is stretching or dilatation, which may be diffuse or may be in the form of local saccular aneurysms.

Syphilitic Arteritis.—Syphilitic arteritis involves the cerebral arteries most frequently, although it is said to occur in other small arteries such as the coronaries and those of the extremities.^{74, 75} Two types of arteritis of the smaller

vessels are described: (1) *Gummatus arteritis*, characterized by nodules with caseous centers, a fibrocellular periphery with epithelioid cells and giant cells occurring in the adventitia or about the perivascular lymphatics. The condition is rare but is best seen in gummatus meningitis. (2) *Diffuse syphilitic arteritis* is more common than the gummatus form.⁷⁶ It is essentially a syphilitic obliterating endarteritis. The artery tends to be hard, white, and cordlike. Cellular proliferation of the intima finally leads to obliteration of the lumen, while the media remains practically unaltered. The adventitia is usually thickened.⁷⁷ (Fig. 407.)



Fig. 406.—Syphilitic mesaortitis. Note the small scars scattered through the media surrounded by round cells. The adventitia is almost as thick as the media, while the vasa vasorum show an obliterating endarteritis.

Tuberculous Arteritis.—Tuberculous arteritis is secondary to tuberculosis of the lungs, kidneys, or some other organ. Commonly, in the lungs, the tuberculous infection invades the adventitia and media of the arteries, resulting in intimal proliferation and finally endarteritis. Thus, arteries in the trabeculae crossing tuberculous cavities are usually sealed off. If caseation occurs in the vascular wall, hemorrhage is likely to result. This is seen most frequently in the caseation of early lesions. Hemoptysis may thus be the first sign of a tuberculous pneumonitis. Pagel⁷⁸ believes that extrapulmonary tuberculosis (tuberculosis of bones, joints, kidneys, cervical lymph nodes, genitourinary tract) may have its origin in a pulmonary lesion which has small subacute tubercles projecting into the lumen of the vessel. Thus small numbers of tubercle bacilli are fed into the blood stream which in time establish smoldering or latent foci in distant organs. (Fig. 408.)

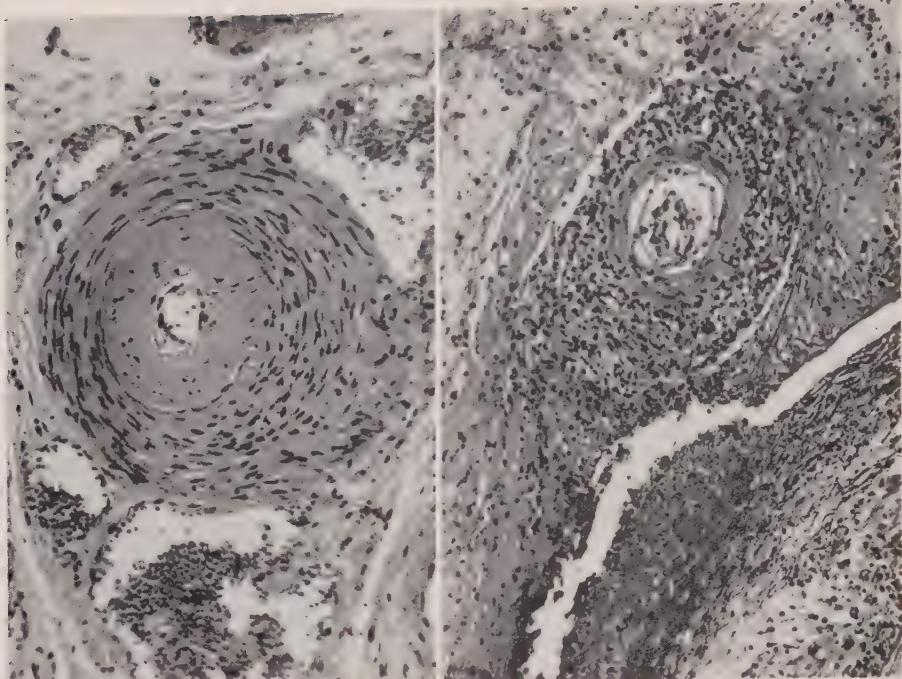


Fig. 407.

Fig. 408.

Fig. 407.—Syphilitic arteritis. Medial and fibrous intimal proliferation, "obliterative end-arteritis," in a pulmonary arteriole in syphilis of lungs.

Fig. 408.—Tuberculous arteritis of meningeal arteriole in tuberculous meningitis. This is probably an allergic periarteritis.

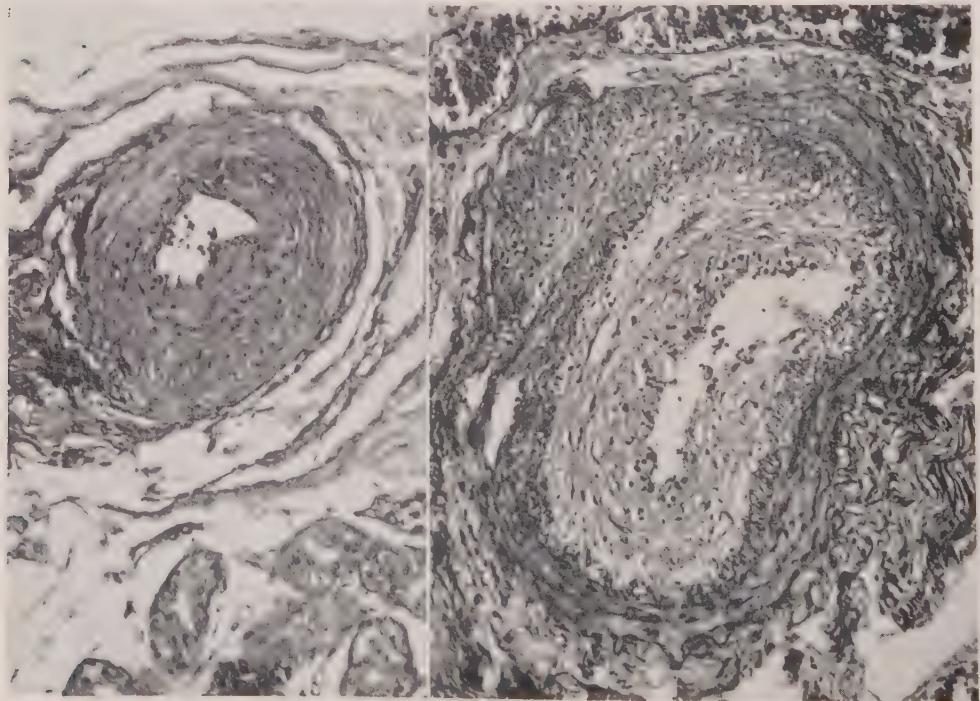


Fig. 409.—Arteries in scleroderma. Intimal proliferation ("endarteritis") in an arteriole of skin (left). Note sweat glands on the lower right. The picture on the right illustrates a similar condition involving the intima of a small artery of the lung.

ARTERIAL LESIONS PRODUCING ISCHEMIC NECROSIS AND GANGRENE OF THE EXTREMITIES

Raynaud's Disease (Primary Raynaud's Phenomenon).—Raynaud,⁷⁹ in 1862, described vasoconstrictive changes in the extremities on exposure to cold. The disease designated by his name is characterized by symmetrical blanching of the finger tips of both hands accompanied by sensations of numbness, tingling, and burning. Blanching is followed by cyanosis and later by redness. Eventually, necrosis or dry gangrene appears in the skin at the tips of the fingers. This series of changes is called Raynaud's phenomenon. Since the lower extremities are seldom involved and the gangrenous lesions are symmetrically distributed, the condition differs from Buerger's disease and arteriosclerotic gangrene—diseases in which Raynaud's phenomenon may occur. In the latter conditions the lower extremities are usually affected unilaterally. Furthermore, Raynaud's disease occurs chiefly in young women (12 to 50 years) in the ratio of 5 females to 1 male,⁸⁰ while Buerger's disease and senile gangrene occur predominantly in men.

The digital arteries are always thickened in long-standing cases, but this is likely due to the effect of the vasospasm. Obstructive lesions may be found in the digital arteries of old severe cases. Only rarely is opportunity afforded to study the arteries in the early stages of the disease. Allen,⁸¹ by the aid of arteriography, found no constant changes in the arteries of Raynaud's disease. Besides ulceration of the finger tips previously mentioned, sclerodermatosus changes may occur in the skin of the fingers. Although in some patients the disease is mild, in others it advances progressively each winter season, eventually producing considerable disability. Sympathectomy cures some patients and affords considerable relief to many.

Secondary Raynaud's Phenomenon.—Raynaud's phenomenon may be secondary to trauma (pneumatic hammer disease, vasoconstrictive phenomena of typists and pianists), to Sudeck's bone atrophy, cervical rib syndrome, arterial occlusion (senile gangrene, Buerger's disease, embolism), intoxications due to heavy metals and to ergot, and to certain diseases such as scleroderma and lupus erythematosus.⁸²

Scleroderma (Acroscleroderma; Acrosclerosis).—The term scleroderma signifies a syndrome characterized by induration, pigmentation, and sclerosis of the skin, associated with loss of weight, asthenia, arthritis, and muscle atrophy.⁸³ The skin is smooth, hard, and wrinkles with difficulty. The pathologic alterations, however, are not necessarily confined to the skin. The author has recently seen a fatal case of scleroderma in which the lungs, liver, and kidneys were involved by a fibrosing process apparently similar to that in the skin. The small arteries and arterioles of the involved organs exhibited an extreme endarteritis, as can be seen in Fig. 409. Weiss and associates⁸⁴ reported nine cases of diffuse scleroderma in which the symptoms and signs indicated cardiac involvement. A peculiar type of myocardial scarring was seen in two patients who died and came to autopsy.

Esophageal lesions occur fairly frequently in scleroderma. Patients complain of cold, clammy, moist cyanotic hands and feet which swell and become painful.⁸⁵ It is possible that the primary lesion is in the vasomotor system since Raynaud's phenomenon is frequently associated with the disease. Scleroderma may, however, precede the vascular changes by months or years.⁸²

Acroscleroderma refers to scleroderma of the extremities, face, and chest, without reference to Raynaud's phenomenon. The etiology of the disease is unknown. The digital arteries may be occluded because of hyperplasia of the intimal connective tissue. Some authors have found thrombi present. The terminal phalanges or even whole fingers may be lost due to gangrene. Trophic ulcers are common. The fingers are very stiff and clumsy and should be protected against trauma and extreme changes in temperature. Sympathectomy may afford relief in the vasomotor types of scleroderma. (See also page 1148.)

Arteriosclerosis Obliterans (Senile Gangrene).—Arteriosclerosis obliterans refers to arteriosclerosis occurring in the extremities which progresses to the state of occlusion of the arterial lumina. It is commonly a disease of older people. It is the commonest of the conditions producing peripheral arterial occlusion. Allen, Barker, and Hines⁸² use the term "arteriosclerosis obliterans" to include arteriosclerosis with occlusion and arteriosclerosis with thrombosis. It also includes the older term "endarteritis obliterans" which is not very clearly defined.

The advanced lesions of the femoral arteries are similar in most essentials to those already described under coronary artery disease. The iliac, femoral, and popliteal arteries are most frequently involved; the posterior and anterior tibials are also commonly affected. Grossly, the vessels vary in thickness, some segments are dilated and tortuous, other segments may be contracted, while brittleness and hardness are characteristic features. Microscopically, there is extensive irregular hyaline fibrous thickening of the intima, interrupted or thinned here and there by atheromas. The lumen is narrowed and usually eccentric in position, due to the one-sided location of the atheromatous process. Atheromatous changes are usually prominent in the larger arteries such as the femoral and popliteals, while in the tibial arteries the incidence of atheroma may be low (Fig. 410). The medial coat tends to show thinning and atrophy, especially when associated with atheromatous lesions of the intima.⁸⁵ Calcification is commonly seen at the edges of the lipoidal deposits within the fibrous tissue of the intima or as extensive deposits within the media. The latter is the result of medial necrosis and calcification and may occur with or without atheromatous changes. It may

destroy most of the medial coat. Fibrosis of the medial musculature is common in areas free of calcification. (Fig. 411.) Ossification occurred in 12 to 45 per cent of calcified plaques in cases reported by Sappington and Fisher.⁸³ Hemorrhage may occur in small vascularized areas adjacent to the lipoid deposits. Clumps of hemosiderin, or macrophages containing it are often present in these areas. Lipophages, likewise, may be abundant about the atheromas. Thrombosis is a dreaded and almost invariable complication of arteriosclerosis obliterans. It is promoted by narrowing of the lumen, ulceration of atheromas on the intimal surface, hemorrhage, and other factors which tend to destroy the endothelial lining. The thrombus may or may not be recanalized.



Fig. 410.

Fig. 410.—Arteriosclerosis obliterans. Marked intimal proliferation ("endarteritis") of anterior tibial artery. An organized thrombus surrounds the larger luminal opening. Negro woman, aged 73 years. Dry gangrene of great toe.

Fig. 411.—Arteriosclerosis obliterans. Note excessive medial calcification of a tibial artery. White man, aged 82 years. Gangrene and cellulitis of great toe, dry gangrene of fourth and fifth toes.

Changes in the tissues due to ischemia are important pathologic features. There is atrophy of the skin and muscles with fatty and fibrous tissue replacement of muscle, loss of subcutaneous fat, fibrosis of digital fat, osteoporosis, and ischemic neuritis. Gangrene develops first in the distal part of one toe, later involving other toes, the foot, and finally the leg, but seldom progresses above the knee.⁸² The skin in the early stages shows a dusky red color which changes to dark blue or purple. In fact,

the color changes of Raynaud's phenomenon are observed in about 10 per cent of the cases.⁸² Finally, the part becomes black and mummified. Such areas of dry gangrene are separated from the living tissue by a red line of inflamed tissue. The inflammation is due to absorption of irritating protein-disintegration products. In the early red stage the toes appear slightly swollen and the overlying skin is shiny. Vesicles may be present.

Symptoms vary from mild to severe, depending on the amount and speed of involvement. *Intermittent claudication* is one of the earliest symptoms in patients in whom the arterial occlusion is not too extensive. It is frequently unilateral at first and is often more pronounced in one leg than in the other. Pain may develop in the foot,

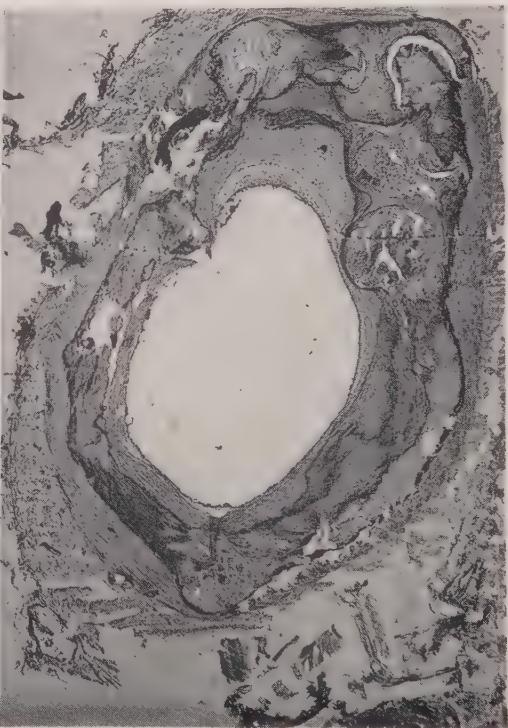


Fig. 411.

calf, thigh, or hips but is commonest in the calf muscles. Pain due to ulceration or gangrene may be severe and persistent.

Absence of arterial pulsation as determined by palpation is one of the most important findings in establishing the diagnosis of occlusive arterial disease. Absence of a pulse in the dorsalis pedis may occur in normal individuals. Pulsations in the posterior tibial, popliteal, and femoral arteries are seldom absent except in occlusive arterial disease. Pallor of the skin on

elevation of the leg and rubor on dependency of the part are pathognomonic of arterial occlusive disease, especially if the difference between the two legs is marked.⁸²

Diabetic Gangrene.—Arteriosclerosis obliterans is an important complication of diabetes mellitus. Warren⁸⁶ found 143 deaths from arteriosclerosis among 484 autopsies on diabetic patients.

Prognosis in arteriosclerosis obliterans is relatively poor. The process in the vascular tree is progressive, and therefore chances for survival of the affected extremity are not good. Much depends on the extent of occlusion, its rapidity, number of collaterals, condition of the feet, extent of trauma. About 35 per cent have hypertension, 20 per cent have diabetes mellitus. Most of the patients are old. In a series of 116 patients studied by Hines and Barker,⁸⁷ 54.6 per cent died within three years of their first visit to the clinic.

Thrombo-angiitis Obliterans (Buerger's Disease).—Thrombo-angiitis obliterans is an inflammatory panarteritis and panphlebitis of the medium-sized and small arteries and venae comites of the extremities, associated with thrombosis and organization. The lesions tend to be segmental in distribution and recurrent attacks are the rule. A complete and permanent occlusion of the affected vessels results, and in turn produces ischemia, malnutrition, and finally gangrene of the affected part. The lower extremities are affected more commonly and more severely than the upper extremities. Blood vessels of the viscera may be involved occasionally.

Etiology.—The disease has been studied intensively for the past forty years, but, in spite of this, no definite cause has been brought to light. Although uncommon, the disease is not rare. At the Mayo Clinic the incidence during a fifteen-year period was 1 in 1,000. In the general population it is about 1 in 6,000.⁸² The disease occurs in young males aged 25 to 50 years. Only a few proved instances have been observed in women. It seems to occur widely among various races, but the incidence is somewhat higher among Jews. **Heredity** appears to have some influence since Samuels⁸⁸ found two sets of three brothers and one set of two brothers who developed thrombo-angiitis obliterans. It has also been observed in identical twins. There appears to be no relation to occupation. A cold climate tends to aggravate the condition, but the disease may occur in the tropics.

The use of *tobacco*, especially cigarette smoking, has an accelerating effect on the progress of the disease. Nicotine is a vasoconstricting drug and probably acts by further reducing the blood supply to the already ischemic areas. Silbert⁸⁹ 1927, states "whatever may be the underlying cause, smoking plays an active role in the production of this disease, and cessation of smoking is the most important therapeutic measure."

Patients who develop thromboangiitis obliterans are usually heavy smokers.

Buerger⁹⁰ believed the disease was caused by some infectious agent. He produced thrombo-phlebitis by transplanting fresh thrombus from a case of thrombo-angiitis obliterans to the arm veins of several volunteers in whom the disease was latent. The veins were first ligated above and below the site of inoculation. The virus theory has not been thoroughly explored but success in this direction seems unlikely. The disease is local without a systemic phase. There is no fever and the condition is essentially chronic with recurrent episodes.



Fig. 412.—Diabetic gangrene of great toe. White female, aged 53 years.

PATHOLOGIC ANATOMY.—The gross appearance of the lesions varies with the age of the process. In the early stages the artery is contracted to some degree in the occluded segment and often in the adjoining nonoccluded parts. The occluded vessel feels hard to palpation. The

lumen is filled with a red or reddish-brown thrombus. In the older lesions the occlusion mass is yellow. The artery is usually involved first, later the vein. In some of the chronic lesions the artery, veins, and nerve are bound together forming a fibrous cord. The occluded segments vary in length; occasionally two or more such segments are present in the same vessel. The *histologic changes* in the acute lesions are seldom seen by the pathologist since his material is obtained from legs or arms that have been amputated because of gangrene. In the acute stage there is proliferation of endothelial cells lining the intima. A recent thrombus fills the lumen. Endothelial cells and fibroblasts are usually present within the thrombus. A few

and is not observed in any other disease. The undulations of the elastic lamina are due to contraction of the vessel following organization of the thrombus. (Fig. 414.) Destructive lesions of the wall, bulging of the wall, and eccentric placement of the lumen such as seen in periarteritis are never found in Buerger's disease. Likewise, atheromatous plaques and calcification of the media play no part in this condition.

Thrombosis and Embolism of Arteries of the Extremities.—Embolism of one of the larger arteries of an extremity causes a sudden occlusion of the main blood



Fig. 413.

Fig. 413.—Thrombo-angiitis obliterans (Buerger's disease) in digital artery of finger. Early proliferative phase in organization of thrombus. Note presence of giant cells.

Fig. 414.—Thrombo-angiitis obliterans (Buerger's disease). Recanalization of organized thrombus. Lymphocytes, fibroblasts, and endothelial cells are present in the central mass. Note the characteristic wavy internal elastic membrane. Gangrene and ulceration of thumb in a 30-year-old white man.

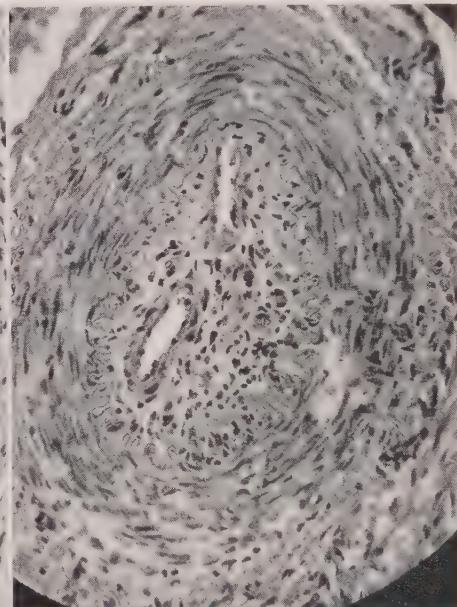


Fig. 414.

collections of lymphocytes and often some polymorphonuclear leukocytes are present within the clot and may also be seen in the media and adventitia. Buerger⁹¹ described giant cells which appear in the periphery of the thrombus in this stage. (Fig. 413.) The internal elastic membrane is well preserved. There is little change in the media other than dilatation of capillaries and infiltration with fibroblasts. The adventitia exhibits fibrous thickening, with lymphocytes often present about the *vasa vasorum*.^{82, 91}

In instances of long-standing affection, the microscopic picture, which includes a thick, wavy internal elastic lamina and occlusion of the lumen by a moderately cellular and weakly recanalized connective tissue is characteristic

supply to the limb. This emergency calls for prompt and intelligent treatment if the extremity is to be saved. The heart is the usual source of such emboli. They may come from a fibrillating left auricle or a mural thrombus of the left auricle or ventricle or from vegetations on the mitral or aortic valves. Arterial occlusion due to thrombosis is usually a somewhat slower process but it may occur suddenly.⁸²

Thrombosis is seen in periarteritis nodosa, thrombo-angiitis obliterans, and in mycotic

arteritis. The latter may result from septicemia, pneumonia, peritonitis, and other acute or subacute infections. Cardiac failure with compensation causes slowing and chemical changes in the venous blood. Increase in the coagulation time of the blood may be a factor. Thrombosis due to arteriosclerosis is common. Trauma is also a factor in stab and gunshot wounds, accidents, cervical rib, etc. (Fig. 403). Post-operative thrombosis may result from propagation of thrombi from small severed branches of an artery.⁸²

The symptoms of acute arterial occlusion are pain, numbness, coldness, and tingling in the affected part. Pain probably due to arterial spasm is the initial symptom in about half of the cases. The arteries most frequently affected are the popliteal, femoral, and brachial.

NECROTIZING ANGIOSES (ANGIITIS)

This group includes lesions of the peripheral arteries characterized by fibrinoid necrosis of their walls. Inflammatory and granulomatous lesions are associated, and thrombosis is usually present. Included here are periarteritis nodosa, temporal arteritis, lupus erythematosus disseminatus, rheumatic arteritis, and malignant nephrosclerosis. While periarteritis and rheumatic arteritis are believed to be due to allergy, no such etiology has been generally accepted for the other conditions. Hueper places thromboangiitis obliterans in this group. Necrosis of media or arterial wall is not a conspicuous part of the picture in Buerger's disease, a fact which differentiates this disease microscopically from the necrotizing angioses.

Periarteritis Nodosa.—Periarteritis nodosa, or polyarteritis, is a necrotizing, inflammatory, obliterative lesion of small arteries, arterioles, and occasionally veins. It is characterized by a segmental necrosis beginning in the media and practically always involving the internal elastic lamina, and by inflammatory exudate including fibrin and eosinophiles. All the other changes are sequelae or complications of necrosis and inflammation. These include thrombosis, organization, recanalization, aneurysm formation with or without rupture, and healing with deforming fibrous scars in the walls of the arteries.

Periarteritis is a disease of unknown etiology occurring predominantly in men and seen in all age groups. The average age is about 37 years.⁹² It is an uncommon disease, 350 cases having been reported up to 1942.⁹³ Infections, toxins, filtrable viruses, and allergies have all been suggested as etiological factors. Rich⁹⁴

produced a closely similar disease in rabbits by single or repeated injections of horse serum with or without the use of sulfanilamide. The occurrence of the disease following use of sulfonamide drugs and its occurrence in individuals with a history of asthma suggest the role of allergy in its production.⁹⁵

PATHOLOGIC ANATOMY.—Grossly, the multiple occurrence of nodose lesions, usually 2 to 4 mm. in diameter, along the course of small arteries is characteristic. The nodosity may be caused either by necrosis and granulomatous proliferation or by aneurysm formation. Aneurysms not infrequently rupture, causing death by hemorrhage. Only rarely does the disease involve the arteries of only one organ. The frequency of involvement of the visceral organs in 87 cases of periarteritis nodosa is presented by Harris and associates⁹² as follows: the kidneys in 87 per cent; the heart in 84 per cent; the liver in 71 per cent; the spleen in 31 per cent; and the lungs in 25 per cent. (Fig. 415.)

The microscopic pattern has been divided into various stages by Arkin⁹⁶ and others. The earliest changes noted are those of edema and fibrinous exudation followed by necrosis of the inner media and subendothelial tissues in the smaller vessels. In somewhat larger arteries there is often a variable zone of necrosis involving the outer media. Usually, the necrotic area stains intensively with eosin so that it has been called hyaline or fibrinoid necrosis. Not infrequently, though, the zones of necrosis may be basophilic, due no doubt to the presence of many bits of nuclear debris. The weakening of the wall of the vessel in this stage may produce an eccentric lumen and bulging of the arterial wall. Fibrinoid changes in the adventitia are common. As Arkin⁹⁶ pointed out from his studies of serially sectioned vessels, the area of necrosis usually forms an ellipse, with the long diameter paralleling the axis of the vessel. Thus, in cross sections any portion of the circumference of the artery may be involved by necrosis. (Fig. 416.) Coincidentally with and following the advent of necrosis, there is infiltration with inflammatory cells. Usually in the early stages neutrophiles predominate, although eosinophiles may be numerous. Later, lymphocytes, plasma cells, and macrophages appear. These cells may be seen in vessels

in which there is little necrosis. Their distribution in all instances includes the adventitia. (Fig. 417.) If necrosis occurs, the internal elastic lamina seems always to be involved. The appearance is rather striking—the lamina is thickened, fragmented, and almost amorphous in character, staining intensely with eosin. The endothelium may be intact or may be desquamated. In the latter instance, thrombosis is likely. In end arteries this leads to infarction. This

liferation of the capillaries and fibroblasts occurs, which results in deforming scars of the vascular walls, often with great diminution of the lumen of the artery. When thrombosis has occurred, organization takes place and usually recanalization follows. Intimal proliferation may be present about the area of destruction, extending for some distance on both sides. This does not appear to be a specific change, as it is seen in other vascular diseases.

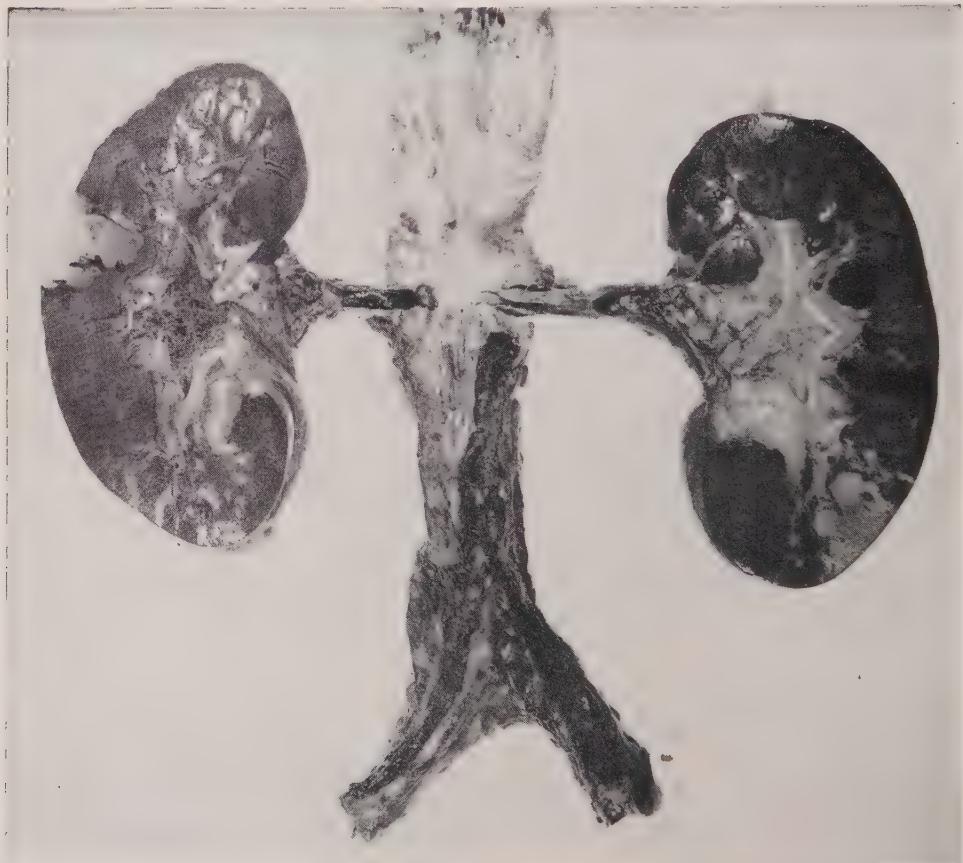


Fig. 415.—Thrombosis of common iliac and renal arteries in a patient with acute periarteritis. Note infarcts in the kidneys.

complication is noted especially in the kidneys, intestines, spleen, and myocardium. Aneurysmal dilatation of the vessel resulting in rupture is the other important complication. The liability of these aneurysms to rupture is due to the paper-thin nature of the viable portion of the media and/or adventitia. In the healing stage mononuclears predominate; pro-

It is now recognized that there is a healed stage of periarteritis in which only the old fibrous scars are seen in the vascular walls. These scars are poor in cells and the lumen of the vessel is obliterated or greatly reduced in size while periarterial fibrosis may be extensive. (Fig. 418.) Accompanying these, may be healed contracted scars in all the organs

involved. Because the disease tends to involve arteries in successive attacks before death occurs, all the stages described above may be seen in the same patient and even in the same organ. The mortality rate approaches 100 per cent.

With such a pathologic background, symptoms of an amazing variety and changeability occur in the various systems involved. Among these are fever, leukocytosis, albuminuria, abdominal pain, hypertension, edema, neuritis, and arthritis. It is of particular note that peripheral involvement with possible subcutaneous nodules occurs in only about 23 per cent. Red blood cells in the urinary sediment may be of particular aid in diagnosis.⁹⁷

than Hutchinson¹⁰¹ in 1890. Horton and his associates⁹⁸ gave the disease the name of *temporal arteritis* and were the first to give the clinical and pathologic findings. It occurs in the older age group, the average age being 65 years. It now appears that sexes are affected equally. All attempts to demonstrate an etiological agent have been unsuccessful. The presence of fever, leukocytosis, and increased sedimentation rate indicate that it is infectious in origin. The *anatomical lesions* are most often present in the temporal arteries. Other than these, they are liable to have a most irregular distribution. A segment of one or both temporal arteries becomes raised, nodular, indurated, and exquisitely tender. The skin over the area is reddened and edematous. Thrombosis may occur but its absence is more common than its

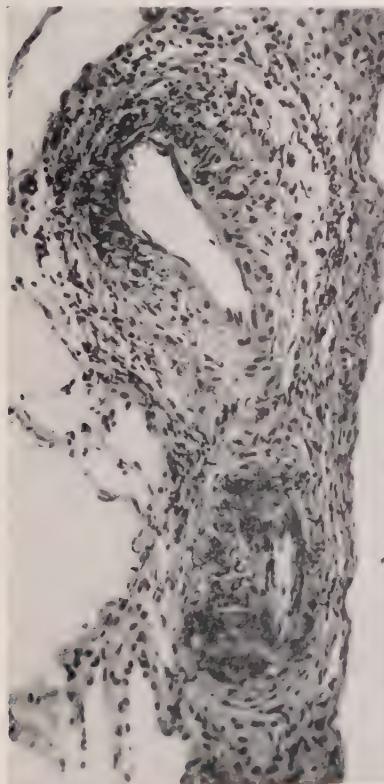


Fig. 416.

Fig. 416.—Periarteritis, acute. The smudgy appearance of the smaller vessel is due to hyaline necrosis. Subcutaneous nodule in 69-year-old white woman.

Fig. 417.—Periarteritis, acute, in a coronary artery. The lumen is filled with an organizing thrombus. The inflammatory cells infiltrating the wall and perivascular tissues are mostly polymorphonuclear leukocytes.



Fig. 417.

Temporal Arteritis.—Temporal or giant-cell arteritis is a febrile, probably infectious, granulomatous disease, involving the temporal, occipital, and other cranial arteries. In 16 of the 75 cases reviewed by Harrison,¹⁰⁰ the disease was considered to be generalized. Involvement of the aorta, carotid, and iliac arteries is not unusual. The first case was reported by Jona-

presence. Blindness was noted in 25 of the 75 cases reviewed by Harrison.¹⁰⁰ The cause of this has not been determined as involvement of the retinal arteries has been proved only once. Ischemia due to the involvement of blood vessels behind the eye is the presumed cause. Cerebral ischemia and rupture of the aorta are other causes of death. *Histologic examination*

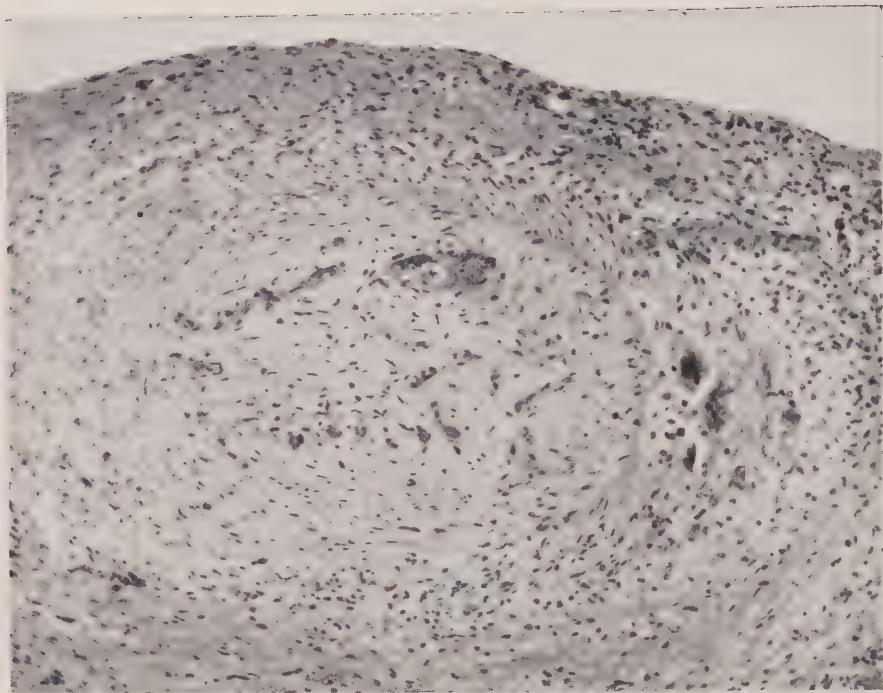


Fig. 418.—Healed stage of periarteritis. The artery is practically obliterated by scar tissue, while only a few inflammatory cells remain.

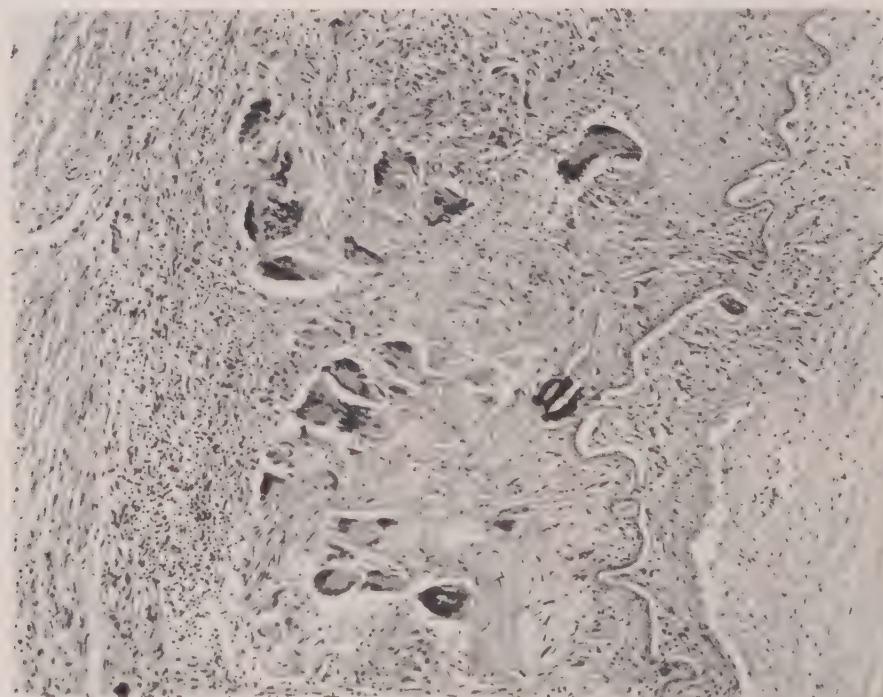


Fig. 419.—Giant-celled arteritis. Internal elastic membrane on the right with intimal fibrosis. Note large giant cells and areas of necrosis in the media. Many round cells are present.

reveals a most severe involvement in the inner layer of the media where areas of patchy necrosis may occur with necrosis and fragmentation of the internal elastic lamina. Characteristically, the multinucleate giant cells in this disease are seen on the medial side of the internal elastic lamina. Lymphocytes are the principal component. Neutrophiles, eosinophiles, and plasma cells may be present. Around areas of necrosis, macrophages are common. Fibroblasts and formation of new connective tissue constitute the healing phase. A great proliferation of connective tissue occurs in the intima resulting in a tiny lumen. The inner portion of the intima is composed of loose connective tissue while the outer portion takes a more active part in inflammatory response, the cellular infiltrate being similar to that of the media. The outer layers of the media are usually less severely involved although occasionally the necrotizing process may involve the full thickness. Changes in the adventitia are usually mild, being composed mostly of infiltration with round cells.

Disseminated Lupus Erythematosus.— According to Klemperer and associates,^{102, 103} this disease is distinguished by widespread collagenous tissue degeneration of a progressive nature and, at the same time, certain characteristic local phenomena. The latter are seen especially in the heart, kidneys, blood vessels, skin, spleen, serous surfaces, and retroperitoneal tissues. The characteristic butterfly lesion on the face in a female patient is helpful, when present, in classifying the disease. We are primarily concerned with the injury to blood vessels observed in lupus erythematosus. The most characteristic change is probably that seen in the spleen, where there is a periarterial fibrosis of the penicillary arteries together

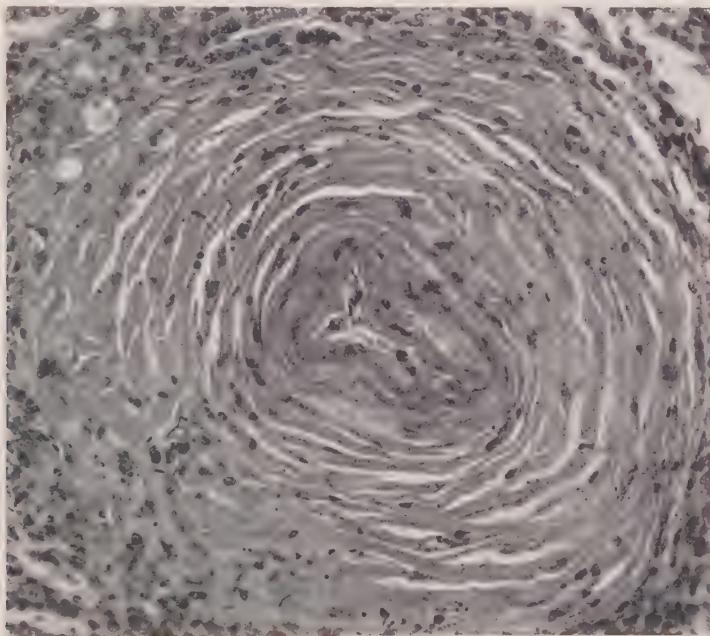


Fig. 420.—Penicillary artery of spleen in lupus erythematosus disseminatus. Note swollen, hyalinized bands of collagen forming an "onion-skin" type of lesion.

SYMPTOMS.—Pain is the outstanding symptom, with tenderness in the affected region. Other complaints are headache, weakness, fever, night sweats, and loss of weight. The course of the disease is variable but usually lasts more than six months.

DIAGNOSIS.—Temporal arteritis differs from periarteritis in the presence of fewer eosinophiles, involvement of larger arteries, absence of fibrinoid change, occurrence of fewer aneurysms, these being localized usually to the head. The patients are older, and the prognosis is good. No successful treatment is known.¹⁰³

with mononuclear cell infiltration. (See Fig. 800, page 917.) Klemperer and associates¹⁰² consider this a specific change (Fig. 420). Fibrinoid degeneration may also be present, superimposed upon the sclerosis. Marked thickening of the basement membrane of the glomerular capillaries, the so-called "wire-loop" lesion, is characteristic when present (Fig. 450, page 570, also page 571).

Malignant Nephrosclerosis.—Malignant nephrosclerosis (Fahr) or "necrotizing arteriolitis" of the renal vessels accompanies so-called "malignant" hypertension. The process in the kidney advances more rapidly and the patients tend to be younger in the "malignant" as compared with the "benign" forms of nephrosclerosis. Two kinds of vascular lesions occur: (1) *Hyperplastic arteriolosclerosis*, due to proliferation of intimal connective tissue or hyperplasia of elastic tissue, may greatly narrow the lumen. The latter is seen more commonly in the interlobular arteries. This group has already been discussed under Arteriolosclerosis, page 516. (2) *Necrotizing vascular lesions* occur only in the malignant form of nephrosclerosis; however, they may occur in pyelonephritis and glomerulonephritis in the presence of uremia.¹⁰⁴ Although the lesion may occasionally be seen in the interlobular and arcuate arteries, it occurs chiefly in the *vasa afferentia* supplying the glomeruli. (See page 567.)

Aneurysms

An aneurysm is a localized abnormal dilatation of an artery due to disease of the media. So-called dissecting aneurysms are more diffuse, often extending the full length of the aorta. *True aneurysms* include the lesions, according to definition, in which one or more layers of the vascular wall are distended. *False aneurysms* are formed by openings in the vascular wall (stab or bullet wounds, acute infections, etc.) producing a hematoma in the adjacent tissues. Soon the blood clot comes to be limited by a layer of platelets and fibrin which later undergoes organization. A capsule may thus be formed about the hematoma which at times is difficult to distinguish from a true evagination of the vascular wall. *True aneurysms* may be classified as primary or spontaneous, traumatic, dissecting, embolic, erosive, arteriovenous, and so-called congenital. True spontaneous aneurysms may be grouped according to form as fusiform, cylindrical, saccular, and cirroid. Spontaneous aneurysms are found most frequently in the aortic arch, and next in the abdominal aorta; the ratio is about 10:1. Next in frequency are lesions of the popliteal, femoral, carotid, subclavian, and innominate arteries.⁷⁷

Etiology.—Aneurysms of the thoracic aorta are usually due to syphilitic mesaortitis. White⁷⁰ thinks that about 90 per cent are due to syphilis. Arteriosclerosis is the next most frequent cause. In the abdominal aorta, arteriosclerotic aneurysm is many times more common than the syphilitic. In the thorax, arteriosclerotic aneurysms are relatively rare. Arterial

aneurysms of the extremities are due to arteriosclerosis, trauma and infection in about that order.

Incidence, Age and Sex.—The prominence of syphilis as a cause of aneurysms of the aorta makes the incidence highest between the ages of 36 to 65 in the white race and 26 to 65 in Negroes, corresponding with the ages when syphilitic aortitis is most prevalent.¹⁰⁵ The ratio of incidence is about 10 males to 1 female.⁷⁰ White presents statistics which show a progressive decrease in the incidence of syphilitic aneurysm of the aorta at the Massachusetts General Hospital in the forty-two-year period from 1896 to 1938.

Race.—The Negro race suffers heavily, due, no doubt, to the greater incidence of syphilitic infection, to inadequate treatment, and to the larger percentage of laborers among Negroes. Aneurysms are three to four times more frequent in this race than in white people.¹⁰⁵

Pathologic Anatomy.—Aneurysms of the aorta are fusiform or saccular in the ascending part, while in the arch itself they are usually saccular. Occasionally, a large fusiform type involves the entire arch. Aneurysms of the ascending arch are slightly more common than those in the transverse arch of the aorta, while they are three times as common as aneurysms occurring in the descending thoracic arch or the abdominal aorta.⁷⁰

The saccular type is more likely to rupture than the fusiform or cylindrical forms because only a part of the circumference of the wall is distended in this type. As the wall continues to stretch, as it does if the opening is large, allowing free circulation and relatively high blood pressure within the sac, it becomes thinner and thinner and finally ruptures. (Fig. 421.) Usually, platelets and fibrin are deposited on the inner wall, especially in the saccular forms. Small aneurysms with narrow openings are often filled with laminated thrombus. This affords considerable protection from overdistention and rupture, especially in the smaller sacs where thrombosis may constitute virtual repair. Thrombi are said to build up from the inner wall of the sac. Blood seeps behind the thrombus and as the wall stretches new laminae are laid down.¹⁰⁶ Aneurysms of the arch may attain huge proportions before rupture occurs. One seen in 1942 at the Los Angeles County Hospital formed a mass the size of a child's head projecting from the anterior chest wall. As the patient sat up in bed, his chin rested on the mass. This aneurysm ruptured through the skin

and caused the patient's death. At autopsy the sac was well filled with thrombus. The wall of a large aneurysm may become paper-thin before it perforates. The inner surface is often rough or fissured, with more or less thrombus adherent to it.

Aneurysms of the ascending aorta reach considerable size. Symptoms and physical signs develop early, while those in the transverse arch or descending portion may remain clinically latent since they tend to bulge posteriorly, producing symptoms referable to the back.¹⁰⁷

exhibit marked destruction of the elastic fibers. Frayed elements persist in isolated areas, but all functional worth is dissipated.

Complications.—Aortic aneurysms produce complications and signs according to their location. Aneurysms at the root of the aorta may be intrapericardial. These compress the pulmonary artery, the right auricle and ventricle. They frequently rupture into the pericardium. Lesions of the ascending part of the arch compress the right lung or right bronchus or erode the sternum and project on the anterior wall of the chest near the midline as a pulsating tumor the size of a man's fist or larger. (Fig. 422.)



Fig. 421.—Syphilitic aneurysm of ascending aorta. The applicator indicates the site of rupture into the pulmonary artery.

Microscopic sections of the aneurysm wall reveal a variegated picture. In older persons more or less atheromatous plaque formation may be found in the intima but the areas are likely to be widely separated. A continuous band of media cannot be found; instead, islands of dense fibrous tissue present themselves, consisting of hyalinized fibrous medial elements separated by elongated triangular or nondescript areas of chronic inflammation. Granulation tissue is present in these areas, heavily infiltrated with plasma cells, lymphocytes, and large mononuclear cells. Elastic tissue stains

These often rupture externally. If they project to the right they may perforate into lung, pulmonary artery, or bronchus. (Fig. 421.) Aneurysms of the arch affect the trachea, producing tracheal tug with each systole, compress the esophagus or recurrent laryngeal nerve. The latter may cause various degrees of huskiness of the voice or even aphonia. A pulsating aneurysm of the dorsal aorta may cause deep erosion of the vertebral bodies, sparing the intervertebral disks which are more resistant. Aneurysms of the lower dorsal or abdominal aorta are smaller, occur less frequently, and are prone to be clinically latent.⁷⁷ The heart is usually not affected by uncomplicated aneurysm of the aorta. It may be hypertrophied, due to other factors such as coronary artery disease, hypertension, or valvular disease. Hypertrophy may, of course, result from complications of the

aortic disease, viz., regurgitation or narrowing of coronary ostia or both.⁷⁰

Arteriosclerotic aneurysms of the aorta are increasing slowly in incidence due to the greater average length of life while aneurysms due to syphilis are decreasing in number because of the lessened amount of syphilitic infection.¹⁰⁵ Ninety to ninety-five per cent of these occur in the abdominal aorta. The ages range from about 65 to 80 years, thus beginning near the upper age limit for syphilitic lesions. The lesion is secondary, as a rule, to severe senile atherosclerosis. The soft atheromatous material becomes washed out of several large plaques in the abdominal aorta, producing ulcers. The blood, in time, dissects within the media for several centimeters, in this way greatly weakening the wall and causing it to bulge from the force of the intravascular pressure to form a fusiform or saccular aneurysm, more commonly the latter.



Fig. 422.—Patient with syphilitic aneurysm of ascending aorta that has eroded through the sternum. The hazy border is due to pulsation of the mass.

These vary in size from that of a tennis ball to a sac as big as a man's two fists. In time, many of these rupture, producing massive retroperitoneal hemorrhage. As the wall stretches, deposits of fibrin tend to fill the sac, at least in part. (Fig. 423.)

Aneurysm of the popliteal and iliac arteries sometimes produce gangrene of the extremity. The same is true probably to a lesser degree of aneurysm of the axillary artery.

Visceral aneurysms are found most frequently in the splenic and renal arteries. A splenic aneurysm may reach the size of a walnut. Preoperative diagnosis has been made in a few instances

by roentgenogram due to the presence of calcium in the wall of the sac. Fortunately splenic aneurysms are rare since operative procedures carry a 50 per cent mortality. Rupture with severe or fatal hemorrhage may occur.¹⁰⁸ Aneurysms of the renal artery may displace the kidney and disturb renal function by kinking or otherwise obstructing the ureters on that side. Perirenal hematoma is difficult to differentiate from ruptured aneurysm of the renal artery. It is usually necessary to remove the kidney. Visceral aneurysms occur in about half of the cases of periarteritis nodosa. Perhaps the small mesenteric arteries are most commonly affected. These arteries are numerous and not well covered, especially in a subacutely or chronically ill patient. Rupture with intra-abdominal hemorrhage is fairly common. The arteries of any organ may be involved, giving rise to false diagnoses of cholecystitis, appendicitis, appendiceal abscess, ruptured peptic ulcer, acute nephritis, cardiac insufficiency, etc.¹⁰⁹

Aneurysms of the pulmonary trunk and its larger branches are rare. Only 116 instances, confirmed by autopsy, are available in the literature up to 1941. The disease occurs equally in the two sexes. Two definite age groups are described: the first group embraces those instances due to congenital anomalies occurring from birth to about 30 years of age, while the second group includes the arteriosclerotic and syphilitic lesions which occur in the years 40 to 60.¹¹⁰

Dissecting Aneurysm of the Aorta.—Dissecting aneurysm refers to a condition in which a tear or other defect in the intima of the aorta allows blood to enter the media, separating it into two layers. The dissection may extend the entire length of the vessel. The blood flows through the new channel in the media or it may flow in both the original and the new beds. However, the new bed is usually filled with clotted blood. The rent or tear occurs, most frequently, 1 to 2 cm. above the aortic valve, while the next area of predilection is at the isthmus near the attachment of the ligamentum arteriosum.¹¹¹ In addition to tears in the intima, defects such as an atheromatous ulcer may be occasionally the site of rupture. In some instances in which no tear is observed in the intima, dissection no doubt begins as an intramural hematoma arising from ruptured vasa vasorum. Amromin and associates¹¹² found arteriosclerotic changes with narrowing of the lumens in the vasa vasorum in 7 out of 12 dissecting aneurysms of the aorta. It is suggested that ischemia of the aortic media is the primary factor in medionecrosis. Hypertension is a com-

mon forerunner of dissecting aneurysm, but syphilis is infrequent in these patients.

PATHOGENESIS.—Attempts to rupture healthy aortas of rabbits or humans experimentally have been largely unsuccessful, even with pressures of 800 to 1,200 mm. Hg.^{113, 114} This would indicate that hypertension alone is not enough. Cystic degeneration and medionecrosis are common findings in this disease. Gsell¹¹⁵ described focal areas of necrosis involving principally the muscle cells and later the connective tissue. The elastic lamellae suffered only minor changes.

sis of elastic and collagen fibers. Nearly all who have reported cases of dissecting aneurysm speak of healing or attempts at healing by fibroblastic proliferation. All agree that cellular infiltration, vascularization, and other signs of inflammation are absent. There is no agreement as to the precise changes in the media, which probably means that the lesion is not uniform but exhibits various types of degenerative change from fatty degeneration to necrosis. In some instances the muscle is first affected, while in others it is the elastic tissue and collagen. The general term medionecrosis is applicable but Erdheim's medionecrosis refers to only one type of change, viz., necrosis of elastic tis-

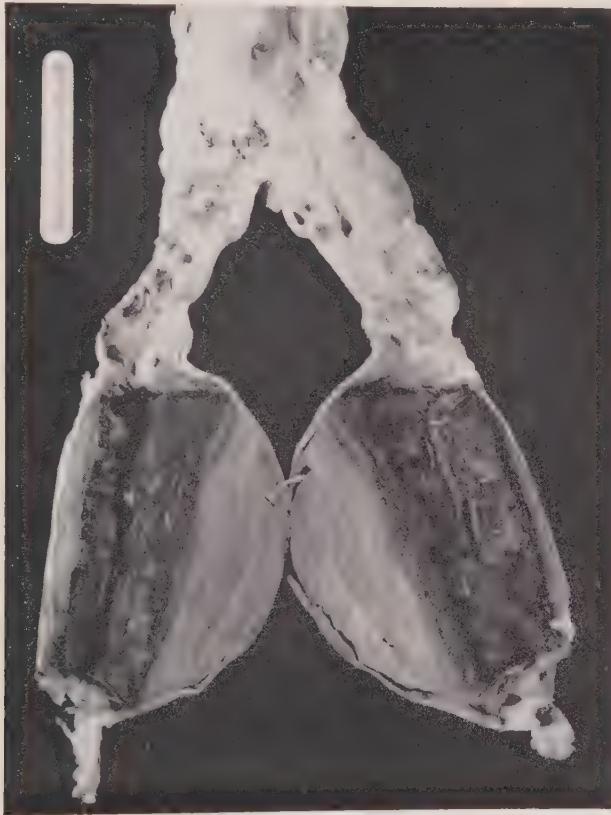


Fig. 423.—Arteriosclerotic aneurysm of the abdominal aorta. The aorta and aneurysm have been split lengthwise to show the laminated thrombus almost filling the sac. Note the channel kept open by the force of the blood stream.

Cleftlike foci often contained mucoid material. Klotz and Simpson¹¹³ made similar observations. Erdheim¹¹⁶ observed sparsely scattered foci of necrosis as indicated by nuclear destruction and, in addition, described numerous focal areas of tissue loss in which elastic and collagen fibers were destroyed while some muscle fibers persisted in the cystic areas. He¹¹⁷ later (1930) described the presence of mucoid material in the cystic spaces (medionecrosis aortae idiopathica cystica) (Fig. 424). Erdheim¹¹⁷ believed that the accumulation of mucoid material in the interlamellar spaces preceded the necro-

sue and collagen with mucoid cyst formation. Medial degenerative changes are found frequently in aortas at autopsy when no dissecting aneurysm is present. The changes are usually mild, as reported by Rottino¹¹⁸ who found some medial degeneration in 95 of 210 unselected aortas examined. The incidence is somewhat higher in hypertensives. Pathologic accumulations of chromotrophic substance are believed to result from aging¹¹⁴ and from degeneration and necrosis of the elastic and collagenous elements of the media where it acts as a "filling substance."¹¹⁹

The etiology of medionecrosis is unknown. The action of adrenalin in producing necrosis of the aortic media in rabbits suggests a toxic action. Duff¹²⁰ produced medionecrosis in animals with diphtheria toxin. Nicotine has been suggested in human cases.¹¹⁵ Hueper¹²¹ and others have observed cystic medionecrosis of the aorta in experimental animals following severe shock from extensive burns.



Fig. 424.—Idiopathic cystic medionecrosis of the aorta. Note the numerous small and one larger cystic spaces in the media containing mucoid material. (Courtesy Drs. Yettra and Lasky.)

LOCATION OF TEAR.—The explanation most generally accepted for localization of a transverse tear of the intima a short distance above the aortic valve is that proposed by Rindfleisch.¹²² He believed the pulmonary artery with its ramifications throughout both lungs affords the chief support for the heart and aorta. He demonstrated bandlike thickenings of the pericardium passing from the pulmonary trunk to the ascending aorta a short distance above the cusps. This constitutes an area of immobilization of the aorta strengthened by the obliterated ductus arteriosus which unites the two vessels. Since the portion

of aorta above these zones of anchorage is relatively mobile, rupture would tend to occur near the site of fixation.

PATHOLOGIC ANATOMY.—Following a break in the intima, or the formation of an intramural hematoma, the blood, as a rule, dissects its way between the outer one-third and inner two-thirds of the media. At first some of the smaller branches given off from the aorta such as the intercostal or lumbar arteries may remain connected with the true channel by slender tubes of intima. As the false space is enlarged by the blood, these tenuous branches become compressed and eventually severed. In dissecting aneurysm involving the entire aorta, larger branches such as the renal, mesenteric, and iliac arteries are dissected for some distance. Occasionally the blood enters a tear near the aortic valve, dissects through the media to the arch, where it again enters the true channel (Fig. 425). The author¹²³ reported a case of this kind that developed in a 17-year-old boy following a mile race. After six months in bed he recovered sufficiently to engage again in athletic sports. He died at 32 of congestive cardiac failure. In this instance the aneurysm which occupied the ascending aorta was completely endothelialized.

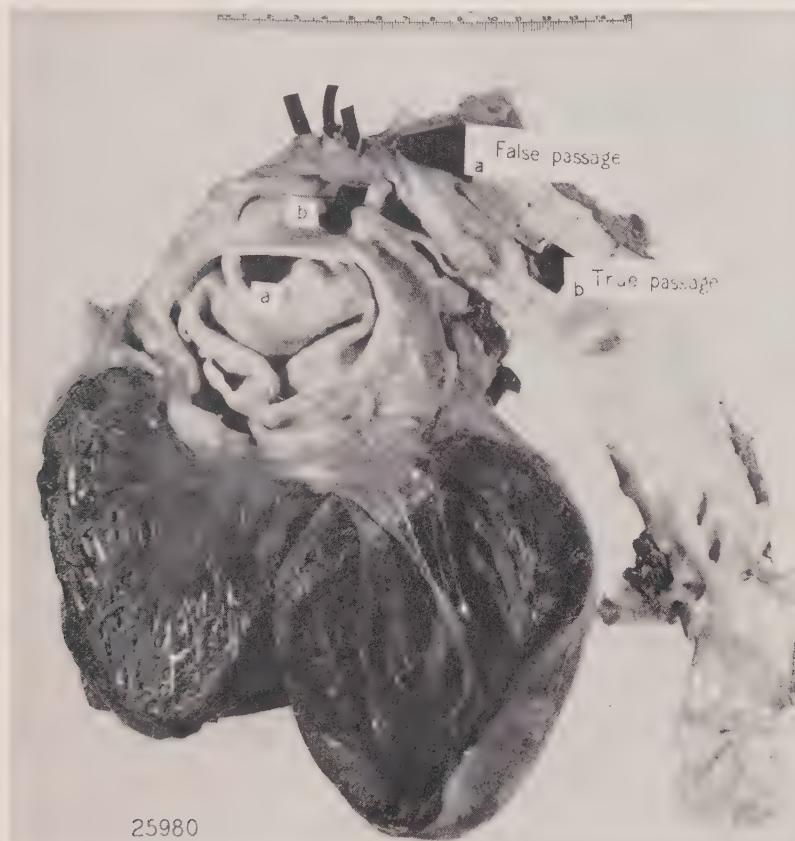
Microscopic studies reveal, in the early stages, widening of the interspaces of the elastic lamellae in focal areas of the media due to infiltration with a homogeneous faintly blue-staining hyaline substance (hematoxylin and eosin stain). The finer elastic fibers have disappeared and even the coarser fibers may be interrupted.¹¹⁷ There may be primary degeneration of the elastic lamellae in the form of fatty metamorphosis, fragmentation and necrosis with or without mucoid accumulations. The interlamellar connective tissue may show hyaline degeneration. On the other hand, the smooth muscle fibers may first show karyolysis and later form a homogeneous mass with the interlamellar collagen. Primary over-production of mucoid substance may reach the stage of cyst formation with loss of all elements of the media in these areas.¹¹⁹ (Fig. 424.)

CLINICAL RELATIONS.—Males are affected predominantly. The greatest incidence falls between the ages of 40 and 60 years. The onset is often

sudden, with agonizing pain of a tearing or rending quality. The localization of the pain varies with the site of the lesion, frequently beginning in the precordial area, spreading to neck or jaws, later to the back, flanks, and legs. The onset may be accompanied by pallor, sweating, and prostration, often with loss of consciousness. The latter may be due to involvement of the carotid arteries. Interference with the blood supply to the spinal cord produces bizarre neurological symptoms and may result in degenerative changes in the cord. Involvement of the renal and mesenteric vessels may cause anemia, hematuria, abdominal distention, ileus, or melena.¹¹¹ Flaxman¹²⁴ found the average duration of life in the recent dissections was 17.6 days, while in the old dissections it was three years.

Quently abetted by hypertension. Miliary aneurysms, on the other hand, are developmental in origin and, therefore, are often called congenital. Forbus¹²⁵ demonstrated defects in the muscular coat of the cerebral arteries occurring in the angles caused by bifurcation of the vessels. Since these defects were observed in otherwise normal cerebral arteries, he believes this arrangement is the usual one. Turnbull¹²⁶ found the medial defect much more common in the cerebral arteries than in other arteries of muscular type.

Forbus¹²⁵ studied a number of small human embryos in serial section, seeking an explanation of the medial defect. He found that the media of the aorta is well formed in the 34 mm. embryo, while some of the branches, such as the intercostals, are merely endothelial tubes within



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Fig. 425.—Dissecting aneurysm of aorta. Note transverse tear in aorta about 2 cm. above aortic cusps. There is a saccular aneurysm in the ascending aorta due to weakening of the wall. Note evidences of dissection on right between the two labels, also farther down in the abdominal part.

Miliary Aneurysms of Cerebral Arteries (Congenital or "Berry" Aneurysms).—Spontaneous nontraumatic subarachnoid hemorrhage occurs fairly frequently. The great majority of such cases are caused by the rupture of a miliary aneurysm of a cerebral artery.

PATHOGENESIS.—Primary intracerebral hemorrhages are usually due to arteriosclerosis, fre-

the mesenchyma. This indicates a separate origin for the media of the larger arteries and their branches and thus may account for imperfect fusion of the muscular coats at the bifurcations. However, the cerebral arteries were not studied directly. Glynn¹²⁷ believes the relatively thick internal elastic membrane of the cerebral arteries is more important than the media in preventing

aneurysm formation. In the light of the foregoing, miliary aneurysms are acquired lesions dependent upon peculiar anatomical defects in the media or degenerative changes in the elastic lamella, or both, which occur at points of maximum intravascular pressures. Hypertension is thus a frequent predisposing factor.

Although miliary aneurysms are the most important of the intracranial group, aneurysms of the larger cerebral arteries may be due to arteriosclerosis. These are fusiform and occur most commonly in the basilar artery (Fig. 426). Others occur in the various branches of the circle of Willis and the proximal portions of the larger arteries given off from the circle.¹²⁸ Trauma, syphilis, acute bacterial and mycotic infections may occasionally cause aneurysms of the smaller arteries.



Fig. 426.—Ruptured aneurysm of basilar artery.

CLINICAL SYMPTOMS.—Spontaneous subarachnoid hemorrhage causes sudden onset of headache followed by coma. Dizziness, nausea, vomiting, and convulsions are frequent symptoms. The neck is stiff. Fever and mild leukocytosis are usually present.¹²⁹

Aneurysms of the common carotid or internal carotid arteries are important since ligation of either vessel for purposes of surgical repair may cause anemia or actual infarction of the brain. Aneurysm of the cervical portion of the internal carotid may be mistaken for a peritonsillar abscess; lancing such an "abscess" may result in fatal hemorrhage.¹⁰⁹

True Traumatic Aneurysms.—Although many traumatic aneurysms belong to the false or spurious group, a small number may be classified as true aneurysms. Traumatic forces that rupture either the adventitia alone or adventitia and media may so weaken the wall that dilatation results. The lesion may be produced by stab, bullet, or shell wounds, fractures, swallowing of fish bones, and the presence of foreign bodies. The aneurysms are usually saccular in form and have a tendency to early rupture.

Embolic and Mycotic Aneurysms.—Simple embolic aneurysms without infection are extremely rare. These are due to the presence in the

blood stream of hard particles such as calcified nodules from the cardiac valves, calcified thrombi, etc., which lodge in the smaller arteries and produce damage to the arterial wall. *Mycotic aneurysms* are due to bacterial infection of the arterial wall usually associated with bacterial endocarditis. The term was adopted by Osler¹³⁰ to emphasize the importance of infection. It is confusing today because it suggests a fungus infection (mycosis) rather than a bacterial infection. Most mycotic aneurysms are embolic in origin and may be called "mycotic-embolic."¹³¹

Erosive Aneurysms.—Erosive aneurysms are due to direct extension of an infective endocarditis on to the aorta or pulmonary artery from the corresponding valve. While these are mycotic aneurysms, they are not embolic. Rupture of the heart may be due to a mycotic aneurysm, usually of the erosive kind.

Mycotic aneurysms are small, as a rule, varying from the size of a millet seed to that of a pea. The larger ones may reach the size of a walnut. They are most common in young individuals up to 40, corresponding with the incidence of acute infectious diseases.¹³² Arteries of all types and sizes are involved. The vessels most commonly affected in order of incidence are: the aorta, the superior mesenteric and branches, the coronaries, and the middle cerebrals and small branches. Infections from within the vessel are due to (1) lodgment of infected emboli in the lumina of the artery or the vasa vasorum or (2) settling of bacteria on the intimal surface. As stated, subacute bacterial endocarditis is usually present. Found in the lesions are streptococci, commonly the green-producing variety, or pneumococci, gonococci, influenza bacilli, typhoid bacilli, and others.

The *histologic* picture varies widely. Characteristically, there is loss of intima and destruction of elastic tissue including the internal elastic membrane, acute or subacute periarteritis, and mesarteritis. Polymorphonuclear leukocytes are often abundant, with masses of bacteria present. In less acute processes, lymphocytes and plasma cells may predominate.¹³²

Infection may enter the artery from some suppurative process in the adjacent tissues, first infecting the adventitia and later extending to the media. A vessel so weakened is likely to show saccular dilatation at that point.

Arteriovenous Aneurysm or Arteriovenous Fistula.—This condition, as the term implies, is characterized by an abnormal communication between an artery and vein. It occurs most frequently in the extremities involving large vessels such as the femoral or popliteal artery and vein. The lesion is usually caused by trauma such as stab, bullet, or shell wounds, flying glass, or occasionally by operative procedures. Rarely, it is due to primary arterial disease, namely, infection, ulceration, or aneurysm.⁷⁰ Congenital arteriovenous aneurysms have been reported.¹³³ Although arteriovenous aneurysms are comparatively rare, they are, nevertheless, important because of the effects produced on the heart and circulation. Much depends on the size of the lesion. Very small communications have little effect, but larger ones permit short circuiting of a considerable volume of blood from the arterial to the venous

system. The pulse slows but the volume output of the heart increases. The left ventricle enlarges and tends to fail if the fistulous opening is large. The vein proximal to the lesion dilates widely and the venous pressure is increased. A continuous, loud, roaring murmur and palpable thrill are evident over the lesion.

Arteriovenous fistulas occur in several forms, depending on whether a direct communication exists between artery and vein, or a sac separates the two vessels at the site of communication (varicose aneurysm). The sac may be located at the side (Fig. 427) with a single opening into artery and vein or with a separate opening into each vessel. The aneurysmal sac may be false or of venous or arterial origin.⁷⁷ Although the vein dilates proximal to the fistula, its wall becomes greatly thickened due to pressure of the arterial blood.

susceptibility to injury during descent through the birth canal combine to localize the lesions here. Some of the cirroids having their origin in birth trauma remain insignificant until later in life, when they may grow rapidly to large proportions. On the other hand, those which appear in adult life may arise from a congenital anomaly.

Cirroid aneurysms are commonly connected with the frontal or temporal arteries. They probably begin as arteriovenous fistulas resulting from trauma or on a congenital basis. As the vessels elongate and dilate, secondary intercommunications may occur. Thus they become larger and more complicated than the usual arteriovenous fistula. They may be destructive of surrounding tissues, eroding the cranium, invading muscle, producing, finally, gangrene and massive hemorrhage.¹⁰⁹



Fig. 427.—Drawing of an arteriovenous fistula of femoral artery and vein caused by a bullet injury. Note the dilated thickened vein above the false passage. The dark saccular structure is an aneurysm of the femoral artery.

Cirroid Aneurysms (Racemose Aneurysms).—The cirroid aneurysm is a mass of dilated, elongated, and intercommunicating arteries and veins.¹⁰⁹ Although cirroid aneurysms are discussed on page 603 they should be mentioned here since not all of them are true neoplasms; in fact, the number of true angiomas is probably small. According to Wagner,¹³⁴ cirroid aneurysm may arise as follows: (1) from a nevus or telangiectasia; (2) from a deep congenital anomaly of blood vessels (deep nevus); (3) from single or multiple traumata. He believes 80 to 90 per cent are congenital and 10 to 20 per cent are traumatic. The scalp is by far the most common location for cirroid aneurysms. The great vascularity of the scalp plus

DISEASES OF VEINS

Congenital Malformations

The chief congenital anomaly is that of aberrant position of the veins. Veins vary greatly in minor detail of branching, but occasionally the main vein or veins draining an organ are in anomalous position. This is usually of little clinical importance except in the case of the long saphenous vein which the surgeon may wish to ligate. According to Dandy,¹³⁵ congenital anomalies of the cerebral veins are common. They are usually associated with malformations of the brain such as macrogryria, microgyria, and rearrangements of the cerebral convolutions.

Degenerations

The veins may exhibit a variety of retrogressive processes such as cloudy swelling, fatty changes in the muscular coat, and necrosis. The first two are of minor importance, but necrosis may be of fundamental concern since, in the larger veins, fatal hemorrhage might result. Necrosis may be due to circulatory disturbances, as in pressure from a large tumor, to infectious agents as in proximity to an abscess, to trauma, radiation, or chemical agents capable of destroying tissue. Thick-walled veins undergo hyalinization but not so commonly as do the arteries. Calcification may occur in focal necrotic areas involving the media or the thickened intima. Occasionally veins are so sclerotic and calcified as to offer technical difficulties in transfusions or intravenous therapy. Hemorrhages may occur within the walls of veins due to asphyxia, severe anemias, or in the course of hemorrhagic diseases. Certain veins that function during fetal life become obliterated after birth. The umbilical veins undergo an obliterating process by which the lumen is closed and the vein becomes a fibrous cord. A similar process often follows phlebothrombosis.⁷⁷

Inflammations

Acute Phlebitis.—In every acute infectious process within the tissues, some of the small veins undergo acute phlebitis. If larger veins are affected, thrombosis ordinarily results. (See page 544.) The infection may come from a distant area and find a foothold in the intima of a vein (endophlebitis), or perhaps more commonly the bacteria enter by way of the adventitia (periphlebitis), passing along the vasa vasorum to the media. This is particularly true of veins which chance to traverse an area adjacent to an abscess. In such an instance, polymorphonuclear leukocytes infiltrate the adventitia of the vein accompanied by hyperemia and edema. The media becomes similarly affected, usually with extension to the intima followed by septic thrombosis. Septic emboli composed of clumps of bacteria, fibrin, and pus cells are likely to be carried to the lungs where new foci of endophlebitis and thrombophlebitis develop, followed in a few days by abscess formation. (Fig. 428.) Occasionally bacteria pass through the capillaries of the lungs to be distributed widely through the systemic blood stream. Staphylococcal infections in children are prone to behave in this manner.

Chronic Phlebitis.—In chronic phlebitis the veins are thickened and fibrous due to chronic inflammation. Most often it is the result of organization and recanalization of a thrombosed vein. There is usually fibrous thickening of the entire wall with atrophy of the smooth muscle and organization of the thrombus. Some areas of round-cell infiltration may be present. The iliofemoral veins may be involved following puerperal infection. The jugular vein may be affected in tonsillitis or due to abscessed teeth.¹³⁶ Chronic phlebitis of the portal vein is seen occasionally following appendiceal abscess or other gastrointestinal infections but is not so common in tuberculosis, syphilis, and perhaps other granulomatous infections.

Phlebosclerosis (Venofibrosis, Hypertrophy of Veins, Productive Phlebitis).—Phlebosclerosis may not be distinguishable grossly from a chronic phlebitis. The vein is thickened, usually smaller than normal, firm, white, and tendon-like. The earlier writers such as Lobstein,¹³⁷ who introduced the term "phlebosclerosis," thought it analogous to arteriosclerosis.¹³⁸ The ages of patients reported by Martin and Meakins¹³⁹ (31 cases) ranged from 18 to 45 years. The relatively young age group of the patients affected, together with the absence of lipoidal and calcific changes in the veins, seem to rule out relationship to arteriosclerosis.

According to Hauswirth and Eisenberg,¹³⁸ the vessels are always small. The usual signs of inflammation are entirely lacking. The histologic changes are uniform, revealing in the early cases loss of endothelium and hyalinization of the denuded surface. The fibrous tissue of the media and, to a lesser degree, the intima undergoes hyperplasia. Thick fibrous nodular masses are frequently observed protruding into the lumen of the vein. Fibrosis may obscure the limitations of media and intima. The small muscle bundles of the media may be surrounded by dense bands of fibrous tissue to produce a rather characteristic picture.

The symptoms are those due to impairment of venous return to the heart. There is often pain and tenderness over the affected vessels especially when the patient is in the erect position. Mottling and cyanosis of the skin of feet and legs may develop on standing.¹⁴⁰

Granulomata.—*Tuberculous phlebitis* is common in tuberculosis of the lungs and is of great importance. Tubercles may develop in the intima if tubercle bacilli are present in the blood (tuberculous endophlebitis), or when a caseous tuberculous tissue such as a lymph node impinges on a vein (tuberculous phlebitis). If in the latter case the infection spreads to the intima, a granuloma or tubercle is likely to form on the intimal surface. When a tuberculous process liquefies and tubercle bacilli are liberated into the blood stream in large numbers, an acute or subacute miliary tuberculosis results.^{77, 141}

Syphilitic phlebitis is of little importance as compared with the arterial lesions of syphilis. In organs such as the liver more or less syphilitic periphlebitis and phlebitis occur about gummatous lesions.

Obstructive Disease of Veins

PHLEBOTHROMBOSIS AND THROMBOPHLEBITIS.—Obstruction in the venous system is commonly due to thrombosis. This occurs more frequently in the veins than in the arteries. In the past, it was supposed that infection most often initiated thrombus formation. Today, stasis and trauma are emphasized as predisposing factors rather than infection. Everyone agrees that when present infection is effective in producing thrombosis. Thus, *phlebothrombosis* has come in to common usage tending to replace the older term *thrombophlebitis*. The latter term is reserved for instances where infection can be demonstrated.

According to Ochsner and co-workers,¹⁴² thrombophlebitis produces clinical symptoms of

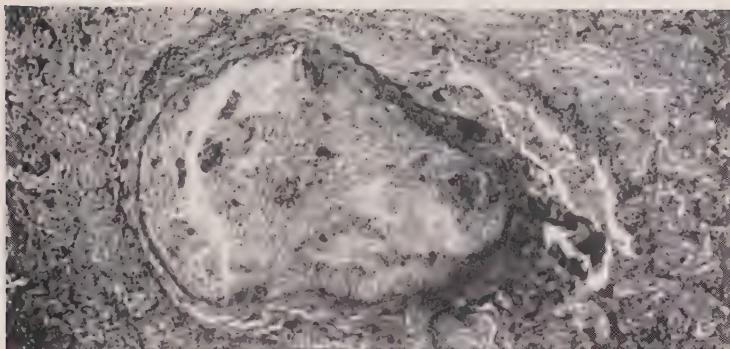


Fig. 428.

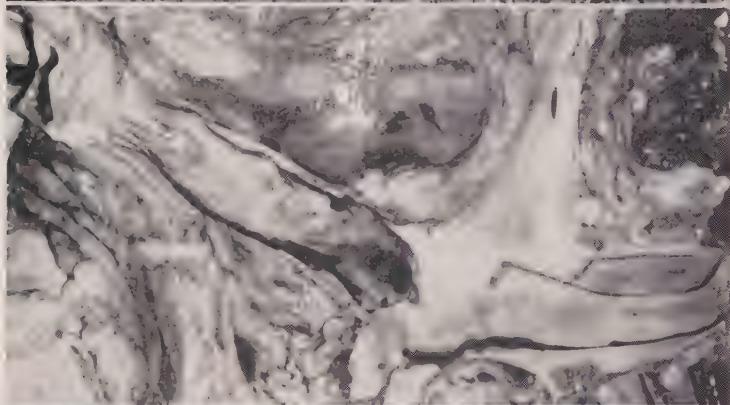


Fig. 429.

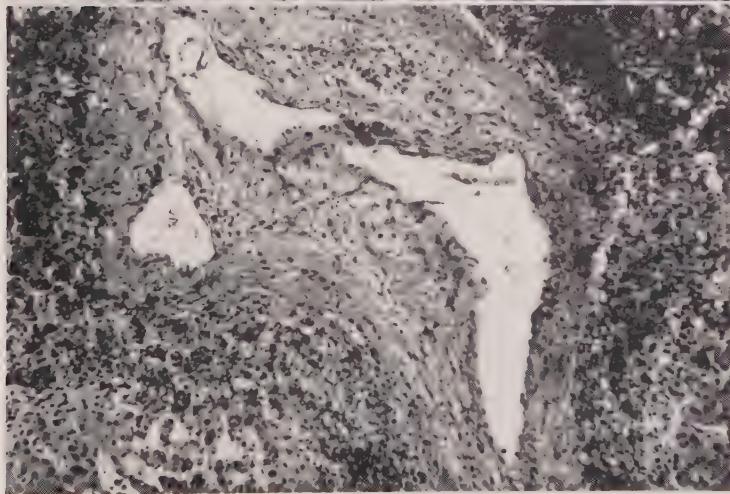


Fig. 430.

Fig. 428.—Thrombophlebitis of pulmonary vein. The small dark spots within the thrombus consist of clumps of cocci (staphylococci). There is hemorrhagic infarction of the surrounding pulmonary tissue.

Fig. 429.—Thrombophlebitis of inferior vena cava and iliac veins. Manual removal of placenta ten hours after birth of child. Death due to pulmonary embolism. Negro woman, aged 29 years.

Fig. 430.—Endophlebitis of hepatic vein (Chiari's disease). Note the peculiar type of intimal proliferation. Atrophy of liver cells is seen in the lower left, hemorrhage in the upper right.

thrombosis, but is not so liable to give off emboli while phlebothrombosis tends to be silent with few or no symptoms until embolization has occurred. Thus, phlebothrombosis is more common and more dangerous to the patient than is thrombophlebitis.

The problem of venous thrombosis is an important one since debilitating or fatal pulmonary embolism occurs in a considerable number of instances. The efforts to reduce the number of these untoward reactions have met with only moderate success. Thrombo-embolism occurs more frequently in the white than in the Negro race and the incidence is higher in men than in women.¹⁴²

ETIOLOGY AND PATHOGENESIS OF VENOUS THROMBOSIS (PHLEBOTHROMBOSIS).—Thrombosis is more common in the veins because of the reduced rate of blood flow in these vessels as compared with the arteries; their thin walls make them easily susceptible to obstruction by pressure, as well as to trauma and infection.

The factors usually listed as essential for thrombus formation are: (1) injury to endothelium, (2) slowing of the blood stream, and (3) alteration in chemical and physical composition of the blood. As early as 1887, W. H. Welch¹⁴⁵ stated and others^{146, 147} agree that changes in the vessel wall are not necessary for thrombus formation. It is true that anatomical changes in the vessel wall may not be demonstrable even by serial microscopic sections.¹⁴⁸ On the other hand, Quick,¹⁴³ and Moolten and associates,¹⁴⁹ maintain that normal endothelium acts as a nonwettable surface and that clumped platelets will not adhere to it. Quick suggests that the changes in the vessel wall may be only minor physicochemical alterations.

As disintegrating platelets adhere to the wall of a vein, a thrombus is rapidly formed according to the reaction outlined. This produces a true corallin thrombus or *head* which is adherent to the vein wall.¹⁴⁶ Clot retraction normally follows clot formation. As the clot retracts, it liberates nascent thrombin which if the blood stream is sluggish, causes further clotting.¹⁴³ The new clot retracts, thrombin is expressed, and further clotting ensues. In this way, a thrombus is propagated forming the *tail* which extends in the direction of the blood flow. Thus, a red clot or tail may be a foot or more in length when formed in the long veins of the lower extremities. This part of the clot is not adherent to the vessel wall and it is this that often separates in the process of phlebothrombosis to produce pulmonary embolization.^{143, 146}

The trauma of parturition, simple fracture, or surgical operation produces an increase in the number of platelets which is roughly proportional to the degree of tissue injury.¹⁴⁶ Simple thrombocytosis does not, in itself, increase the incidence of thrombosis. Thrombosis is frequent in certain blood dyscrasias of which polycythemia vera and leukemia are the most important. The former causes increased viscosity of blood due to the greatly increased number of red blood cells. In leukemia, increased viscosity may result from the increased number of white blood cells.

Unlike coagulation that may take place *in vitro* or *in vivo*, thrombosis occurs in only one

environment—that of the blood stream of a living animal. This is prevented by a protective mechanism which under ordinary circumstances functions efficiently and silently. Proper function is dependent on "maintenance of a blood flow through the vessel of such force and velocity that any appreciable local accumulation of thrombokinase is rapidly washed away."¹⁴⁶ At the same time, the moving stream probably insures against anoxia and other conditions that may damage the endothelium.

General circulatory and respiratory efficiency are of paramount importance in maintaining the peripheral venous flow. A narrow margin exists between flow and stasis in the extremities of a bedridden patient. An ageing or failing myocardium may reduce the left ventricular contraction sufficiently that the rate of flow approaches zero. Reduction in the respiratory excursions plus general muscular immobility make stasis likely and venous thrombosis almost inevitable. The process begins, as a rule, in the veins of the calf muscles and may extend to the larger veins of the leg and thigh. Rössle¹⁵⁰ demonstrated thrombi in calf muscles in 27.1 per cent of an autopsy series. McLachlin and Paterson¹⁴⁸ dissected leg veins and pulmonary arteries in 100 routine autopsies. Thrombi were demonstrated in veins of the legs in 34 per cent of the cases and pulmonary embolism resulted in 56 per cent of these cases.

Dock,¹⁵¹ Hunter,¹⁵² Neumann,¹⁵³ and others have written on the ill effects of bed rest especially for the aged or postoperative patient, since it is believed to be responsible for much of the venous thrombosis of the extremities. Immobility of the lower extremities, with pressure on calf muscles due to the recumbent position, slowing of the venous blood stream during bed rest in both medical and postoperative conditions tend to produce thrombosis of calf muscles with propagation to the veins of thighs and iliacs often culminating in pulmonary embolization. Neumann¹⁵³ in 1938 found venous thrombosis of the legs in 100 of 165 unselected consecutive autopsies. Ochsner and associates¹⁴² reported on 580 cases of venous thrombosis, of which 316 were complicated by pulmonary embolism, 203 ending fatally.

PATHOLOGIC ANATOMY.—Sections through the head of a long thrombus in the veins of the lower extremities consist of a small platelet clot which is hyaline, structureless, and pink-staining with the usual hematoxylin-eosin stain. Built upon this primary clot is a true corallin thrombus which may or may not completely occlude the lumen. The clot is adherent to the wall, at least over part of its surface. The tail part is a red or erucor clot consisting mainly of red blood cells. If the thrombus remains in place, the head portion becomes organized by invasion of fibroblasts and new capillaries that arise from the wall of the vein.

In thrombophlebitis the extremity is usually swollen and the occluding thrombus is firmly attached to the wall of the vein. The wall is thickened and on microscopic examination, it is edematous and infiltrated with polymorphonuclear leukocytes or with lymphocytes.¹⁴⁸

Organization progresses from the periphery toward the center of the clot. Usually recanalization provides a number of small channels which allow a reduced blood flow through the vessel. Collateral circulation is usually adequate except in the iliofemoral area. Reaction to chemical trauma produces, as a rule, complete organization resulting in a fibrous cordlike structure which fails to recanalize.

PATHOLOGIC PHYSIOLOGY.—The degree of obstruction to venous flow depends on the size and location of the vessel affected, together with the extent of the thrombosis. If anastomoses are rich, no serious disturbance follows. Obstruction high up in the iliac or femoral veins is likely to cause considerable interference with venous return. Allen, Barker, and Hines⁸² state that the pressure in the long saphenous vein in cases of thrombosis may reach 162 to 342 mm. H₂O, with the patient in a recumbent position. The normal pressure is 40 to 110 mm. H₂O.

Thrombophlebitis may occur in the puerperium (phlegmasia alba dolens) but is not frequent except in cases of induced abortions. Infections with streptococci or staphylococci are fairly common under these circumstances. (Fig. 429.) Iliofemoral thrombophlebitis is more common in young males and nonpregnant females who are suffering from debilitating disease causing long confinement to bed, or those suffering from infectious diseases, the post-operative state, or trauma, than it is in the postpartum patient. Homans¹⁵⁴ and others have emphasized the importance of lymphatic obstruction in thrombophlebitis. He believes the edema causing the swelling of the arm or leg is due to inflammation and obstruction of the lymphatic drainage.

THROMBOSIS OF DURAL SINUSES.—See discussion on page 1330.

THROMBOSIS OF THE SUPERIOR VENA CAVA.—Obstruction of the superior vena cava produces increased venous pressure in the veins of the head and neck, resulting in edema and cyanosis of the upper part of the body accompanied by dyspnea and cough. Stasis in the cerebral vessels causes headache, vertigo, and somnolence. Thrombosis is one of the less frequent causes of this syndrome. About 120 records of superior vena cava thrombosis may be found in the literature.¹⁵⁵ Ochsner and Dixon found on analysis of these cases the following etiological factors: phlebitis, 36.6 per cent; external compression, 29.1 per cent; mediastinitis, 23.3 per cent; and cause unknown, 10.8 per cent.

THROMBOSIS OF THE INFERIOR VENA CAVA.—Two important signs of this condition are edema of the lower extremities and development of characteristic collateral circulation. Slow occlusion is compatible with long life. The presence or absence of albuminuria helps to determine the location of the thrombus. Albumin indicates thrombosis above the entrance to the renal veins.¹⁵⁶

THROMBOSIS OF THE PORTAL VEIN.—This condition is associated most frequently with cirrhosis of the liver. Other contributing factors are swelling of the periportal lymph nodes, infections of the gastrointestinal tract, or malignancies of the pancreas or liver. Complete

acute occlusions may cause death from infarction of the small bowel.¹⁵⁷ Chronic portal occlusions may run a longer course, up to twenty years, producing symptoms of ascites, abdominal pain, hematemesis, and splenomegaly. Changes in the vein range from those of an impervious fibrous cord to replacement by an angiomatic mass up to the size of a goose egg.¹⁵⁸

The more specific causes of portal thrombosis are: (1) *Primary* changes in the wall of the vein as in phlebosclerosis, often with calcification. This process may begin in the splenic and involve the portal by extension. Or the changes in the vein wall may be (2) *secondary* to infections of the gastrointestinal tract and spleen. Appendiceal abscess is probably the chief cause, producing a suppurative pylephlebitis frequently terminating in multiple liver abscesses. Scarlet fever, pneumonia, typhoid fever, and bacterial endocarditis are some of the general infections that may be responsible for portal thrombosis. Puerperal and other female genital tract infections serve also as etiological factors.¹⁵⁹ (See also pages 205 and 1083.)

THROMBOSIS OF THE HEPATIC VEINS (CHIARI'S DISEASE).—Chiari (1899) described several cases of what he called endophlebitis of the hepatic veins. Only about 70 cases had been reported in the literature to 1946.¹⁶⁰

In all but one of the cases reported originally by Chiari there was an obliterating endophlebitis of the hepatic veins usually beginning in the larger radicals, often extending to the inferior vena cava. The smaller branches were affected in some instances. The chronicity of the condition was indicated by the presence of collateral anastomoses with the umbilical veins, with those of the gastrohepatic ligament, and those in adhesions to the liver capsule. Narrowing of the veins was due to intimal thickening which varied from a loose fibrillary structure to that of dense fibrous tissue. Infection was present in three of the seven cases reported—acute pleurisy of the right side in one and chronic peritonitis in two.

Grossly, the liver appears smooth, congested, swollen, and extremely firm. On the cut surface, areas of congestion alternate with irregular yellow patches of fatty degeneration. The hepatic veins are usually obliterated or greatly narrowed as they approach the vena cava. The endophlebitis frequently affects the vena cava as well. *Microscopic* examination reveals, in the usual case, marked congestion with atrophy and necrosis of the central parts of the hepatic lobules. Endophlebitis obliterans and thrombi in various stages of organization are present in the radicals or the main hepatic veins. (Fig. 430.)

The disease occurs with equal frequency in the two sexes, usually between the ages of 20 and 40 years. It occurs in both acute and chronic forms. In the acute form the onset is sudden, with abdominal pain, nausea, vomiting, and shock, followed by ascites, tenderness and enlargement of the liver and spleen, delirium, coma and death, in one to four weeks. The acute phase may be due to terminal thrombosis of hepatic veins already narrowed by endophlebitis. In the chronic form the onset is more gradual, with epigastric pain, ascites, tender enlargement of the liver, and development of

collateral circulation. Jaundice is rarely observed. Coma, delirium, and death occur in about six months. A variety of etiological factors have been suggested for hepatic vein obstruction. These include primary thrombosis or thrombophlebitis; local or general infection; and mechanical obstruction by congenital anomaly or neoplasm.¹⁶²

Pulmonary Embolism.—Pulmonary embolism is the complication feared by the physician whose patient has phlebothrombosis. Lodgment of a small pulmonary embolus may give the first clinical sign of the presence of phlebothrombosis. Following propagation of the thrombus into a larger vessel, there may develop a fatal or severe pulmonary embolism. When a thrombus has been formed for 3 to 4 days, organization is usually sufficient to prevent it from breaking away. Histologic examination of fatal pulmonary emboli fail to reveal evidences of organization. If this were not true, anticoagulant therapy would be of little avail since it may prevent formation of new thrombi but does not affect thrombi already formed.

Varicose Veins (Varices, Varicosities)

A varicose vein is a dilated tortuous vein. Varicosities occur principally in the superficial veins and their tributaries in the lower extremities, although the communicating veins and even the deep veins may be involved.¹⁶³ The superficial veins are more vulnerable than the deep veins because of their location in the subcutaneous fat which affords comparatively little support. Of the superficial veins the internal or long saphenous vein is most frequently affected.

Varicosities of the lower end of the esophagus are frequently encountered in cirrhosis of the liver due to portal vein obstruction. Fatal hemorrhage into the gastrointestinal tract due to rupture of a varix accounts for about 25 per cent of the deaths in this disease. Varicosities of the pampiniform plexus and the hemorrhoidal veins are common.

Etiology.—Two kinds of varicose veins are recognized: (1) primary or spontaneous, which arise due to inherent weakness of the veins; and (2) secondary varicosities that arise as a result of varying degrees of venous obstruction. A number of predisposing factors are concerned in the production of varices. It is generally agreed that persons in whom varicose veins develop have an hereditary predisposition. The condition is familial in a considerable percentage of individuals, as shown by Larson and Smith,¹⁶⁴ who found a positive family history in 43 per cent of 491 cases. Phlebitis and thrombophlebitis of the iliac veins are factors in causing weakness of the wall or obstruction. Orthostatism is important since intravenous pressure increases greatly when a person is standing. Rutledge¹⁶⁵ found venous pressures taken with the patient in the erect position increased about ten times over those in the recumbent position. Varicose veins appear to be more common in obesity and in old age. Loss of tone may be important in the latter condition. Varicosities are six times as prevalent in women as compared with men,¹⁶⁶ but much of this

increase is due to pregnancy. Pratt¹⁶⁷ states that 65 per cent of varicosities are the result of pregnancy.

Pathologic Anatomy.—According to Ochsner and Mahorner¹⁶⁶ there are several changes of importance in the development of varicosities: (1) elongation and tortuosity; (2) loss of elastic tissue; (3) dilations or ectasia; (4) variations in thickness of the wall; and, finally, (5) changes in the valves. Tortuosity is characteristic of varicose veins and is due to the increase in length. Lack of elasticity is due to degenerative changes in the wall and fibrous tissue replacement of much of the elastic tissue. Dilatation is always present but is variable in degree. Insufficiency of the valves results from dilation of the vein and atrophy of the valves. The walls of varices are thinner than normal in places and greatly thickened in other segments. Perforation may occur in excessively thin areas. Increased pressures tend to produce hypertrophy of the muscularis. Fibrous thickening of the intima is commonly noted on microscopic examination.

Complications.—Complications arising as a result of varicosities are due primarily to stasis within the veins and poor nutrition from relative anoxia. The most frequent complications are edema, dermatitis, ulcer, thrombosis, and hemorrhage.¹⁶³

TUMORS OF BLOOD AND LYMPHATIC VESSELS

Tumors of Blood Vessels

Since in the body blood vessels are ubiquitous structures, they possess less natural autonomy than most organs and, therefore, may be expected to display pronounced neoplastic characteristics. The mechanical pressure of the circulation has considerable influence on the growth of vascular neoplasms.¹⁶⁸ The majority of vascular tumors are benign. Much confusion exists in the classification of these tumors. Because of the variety and complicated structure of many vascular tumors, an excessive number of terms has been used in the designation of any given tumor. *Angioma* is a benign tumor composed of newly formed vessels. Blood vessel and lymph vessel tumors are included—hemangiomas and lymphangiomas, respectively.¹⁶⁸

Hemangioma.—True hemangiomas are thought to be of congenital origin arising by embryonic sequestrations of mesodermal tissue. Growth occurs in the usual way by buds of endothelial tissue which form solid cords. These canalize and establish communication with the parent vessel.¹⁶² There is usually an afferent and efferent vessel connecting

the tumor with some systemic blood vessels. As the tumor grows, it does so by compressing the surrounding tissue and not by involvement of preformed blood vessels, except in the racemose type.¹⁶⁹ These tumors may arise from arteries, veins, capillaries or lymphatics. The great majority appear to be capillary or venous in origin. In some the endothelial lining cells proliferate, while others are characterized by the presence of heavy fibrous or loosely constructed cellular partitions separating the blood spaces. Many of the small capillary angiomas are acquired. Since many of the tumors of the blood and lymphatic vessels occur in the skin, a discussion of these tumors will be found in the chapter on the skin (see page 1171).

LINDAU'S (VON HIPPEL'S) DISEASE.—Von Hippel¹⁷¹ described an isolated angioblastic lesion of the retina in 1903. Lindau¹⁷² (1926) found an associated angioma of the cerebellum or brain stem in 20 per cent of the recorded cases of von Hippel's disease. Syringomyelia and hydromyelia may be associated. Cystic disease of the kidney, pancreas and liver as well as hypernephroma may occur in association with Lindau's disease.¹⁷³

RACEMOSE HEMANGIOMA, CIRSOID ANEURYSM, CONGENITAL ARTERIOVENOUS FISTULA.—These rare lesions are pulsating, bone-eroding vascular tumors with a "Medusa-head" tangle of vessels. They are essentially complicated congenital arteriovenous fistulas. Other types such as cavernous hemangioma and port-wine stains may be associated. Shuck¹⁷⁴ found that 84 of 87 collected cases occurred on the head, usually connecting with the carotid artery. The successful treatment of this tumor offers many difficulties.

HEMANGIOENDOTHELIOMA.—Although the terminology is confused, in general, these are angiomas that exhibit malignant proliferation of endothelial cells about the vascular spaces. Obviously,

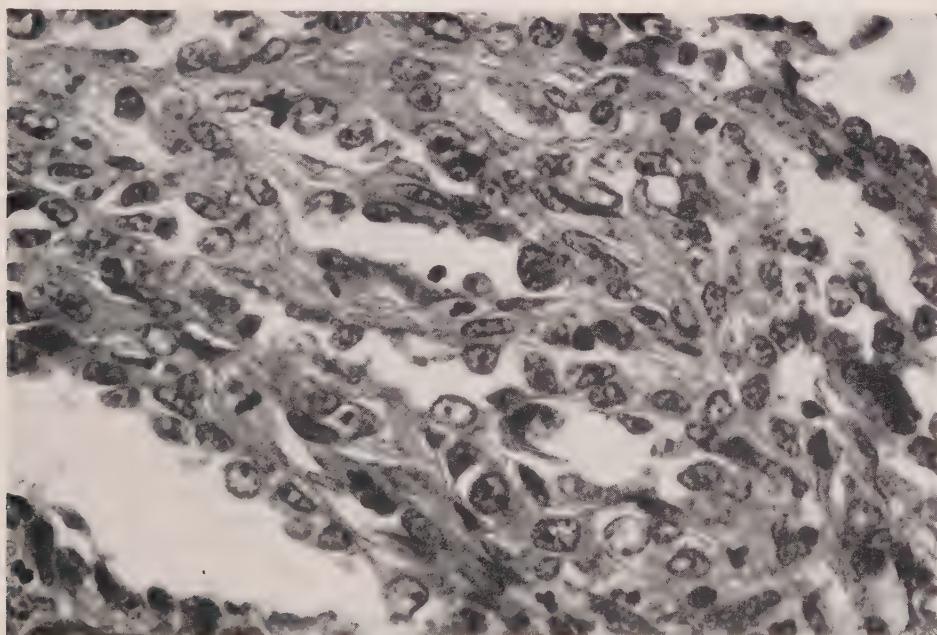


Fig. 431.—Malignant metastasizing hemangioma. Note large anaplastic tumor cells. Several mitoses are present. ($\times 700$.)

CAVERNOUS HEMANGIOMA.—Cavernous hemangioma is a common vascular tumor composed of large venous chambers or cavernae lined with vascular endothelium and filled with blood. The fibrous stroma is scanty. Although they may occur in any of the soft tissues, they are common in the liver where they appear as slightly raised, blue-black areas. These tumors occur also in striated muscles and in bone.¹⁷⁰ *Plexiform hemangiomas* are composed of arterioles and small veins. The small vascular spaces are lined with endothelium. The fibrous wall is relatively thick, including some adventitial fibers.

no clear-cut differentiation can be made between some types of hemangioma and hemangioendothelioma. These tumors occur anywhere in the skin, the subcutaneous tissues, and at times in bone. Occasionally, almost the entire liver or spleen may be involved. On surfaces of skin or mucous membrane they may measure 1 to 20 cm. in diameter. The tumors appear somewhat raised and dark red in color. The histologic picture demonstrates capillary spaces and blood sinuses surrounded by large clear cells with small vesicular nuclei. The cells may be irregularly arranged or they may form mosaic

cell nests about the blood spaces. Mitoses may be present. The degree of malignancy is variable—some grow slowly and metastasize late while others grow rapidly and metastasize early by way of the blood stream.⁸²

Metastasizing hemangiomas are rare malignant tumors of the cavernous angioma type. In a case reported by the author in a white woman of 40 years, the largest tumor was in the right lung although multiple tumors were present in both lungs, mainly in subpleural position. Other tumors were found in the liver and retroperitoneal lymph nodes near the head of the pancreas. Death was due to massive hemorrhage into the right pleural space. The histologic picture varied from typical benign cavernous hemangiomatic structures to extremely cellular areas consisting of large, anaplastic endothelial cells surrounding small vascular spaces. Mitoses were present. (Fig. 431.) Up to 1935, only about a dozen such tumors had been reported in the literature.¹⁷⁵

Tumors of Lymphatic Vessels

Lymphangioma is a tumor composed of lymph vessels.¹⁶⁸ It is an organoid structure consisting of endothelial cells and supporting connective tissue, both of which participate in the neoplastic process. Lymph nodules or round cells are usually present. Islands of fat cells and proliferating smooth muscle cells may be present in the septa. Lymphangiomas are usually slow growing and are frequently congenital.¹⁶⁸ They appear in the skin, deep areolar tissues, and muscles of the neck, trunk, lips, tongue, eye, and orbit as well as the mediastinal and retroperitoneal regions. To distinguish lymphangioma from lymphangiectasis is more difficult than separating true and false hemangioma.

The classification by Wegner¹⁷⁶ is simple and apparently adequate. He divided lymph-vessel tumors into three types: the simple, the cavernous, and the cystic. *Simple lymphangiomas* are rare congenital tumors which appear in the skin or mucous membranes soon after birth. They are small, circumscribed, and warty in appearance. Following trauma they exude a serous fluid. The histologic structure consists of a network of spaces of small and medium size, lying in the derma with thin relatively acellular septal partitions. The lining endothelium may be flat or cuboidal. They grow slowly or remain stationary.⁸²

Cavernous lymphangioma occurs usually in the skin but also in the mucous membranes and intermuscular septa. The dilated lymph spaces are filled with coagulable lymph, at times mixed with blood. The contents may be solidified and even calcified.¹⁶⁸ Analysis of the fluid may reveal blood-proteins and salts, lymphocytes, exfoliated endothelial cells, and cholesterol crystals. The

septa may be thin and poor in cells or they may be thick due to proliferating connective tissue, and the presence of round cells, lymph follicles, and smooth muscle.

Hygroma Colli Cysticum, Axillare and Inguinale.—Hygroma is a benign, true neoplasm of lymphatic origin. It is a multilocular cystic tumor, the cavities of which are lined by lymphatic endothelium.¹⁷⁷ Goetsch¹⁷⁷ reported 12 cases of cystic hygroma, 10 of which were cervical and 2 axillary. Occasional inguinal hygromas have been reported. Although many theories as to etiology have been proposed, Goetsch believes that the tumors arise from sequestrations of lymphatic tissue. In cervical hygromas sequestrations may be derived from primitive jugular sacs which have failed to join the lymphatic system in the normal manner. Hygromas have a potentiality of almost unlimited growth, which is believed to be due to the fact that these "lymphatic nests" retain their embryonic power of irregular growth.

The gross appearance in the early stages is that of a rounded cystic mass, usually in the neck, varying from the size of a marble to that of a golf ball. Most of the tumors grow slowly, often with periods of quiescence. They are noticed at birth or in early childhood in the majority of cases, but occasionally they appear in adults. Pressure of the fluid within the cysts forces extensions into planes and spaces between the muscles and vessels of the neck or into the mediastinum. In this manner the tumors may eventually reach the size of a child's head. By careful histologic studies Goetsch believes he has demonstrated that hygromas grow and propagate by proliferation and sprouting of endothelium and connective tissue from the walls of the cysts. Sprouts of fine endothelial fibrillae grow out into clefts in adjoining tissue, and droplets of lymph-like secretion similar to that in the larger cysts accumulate within the tissue sprouts. The droplets enlarge and thus cause the fibrillae to spread apart and canalize. This is surely a unique way for a benign growth to extend into adjacent tissue. This peculiar manner of extension explains also why hygromas recur if not removed in toto. Symptoms are those due to pressure on various structures as the tumor enlarges. Radical surgical removal is the accepted treatment.

DISEASES OF LYMPHATIC VESSELS

Anatomy

The lymphatic capillaries form a complex system of branching tubes characterized by marked variation in diameter and thinness of walls. Alternate dilations and constrictions of the capillaries produce a beaded effect.¹⁷⁸ The walls of the lymph capillaries consist of thin endothelial plates whose chief function is retention of lymph. Lymph is a colorless fluid of essentially the same composition as blood plasma. It contains lymphocytes and a few polymorphonuclear leukocytes and red blood cells.

According to Gray¹⁷⁸ the larger lymphatic vessels are composed of three coats correspond-

ing to those of the veins. The *internal coat* is a thin, transparent one composed of elongated endothelial cells with wavy margins by which contiguous cells are dovetailed into one another. The cells are supported on a thin elastic membrane. The *middle coat* consists of smooth muscle and fine elastic fibers, arranged in a circular manner. The *external coat* is composed of connective tissue intermixed with smooth muscle fibers disposed longitudinally or obliquely. In the smaller vessels there are no muscular or elastic coats so that the wall consists of a plate of endothelial cells formed into a tube supported by a few connective tissue fibers.

The larger lymphatic vessels are supplied by nutrient vessels and nonmedullated nerve fibers which are distributed to their outer and middle coats. Valves occur in all but the small lymphatic capillaries somewhat more abundantly than in the veins. The beaded appearance of the lymphatics is due to valves which are located at the narrower segments of the vessels. Lymph is propelled by contractions of the skeletal muscles, backflow being prevented by the valves.

Mammals possess a complicated system of lymph vessels which are closed peripherally. These are especially numerous in the superficial tissues such as the skin and mucous membranes. There appears to be disagreement on the extent and location of lymphatics in voluntary muscle.¹⁷⁹ It seems to be agreed that lymphatics of the lungs do not actually reach the pulmonary alveoli but end at the atria. It is also stated that the ultimate functional unit of the liver, the lobule, is not supplied with lymph vessels. Fluid that passes the endothelium of the liver sinusoids passes into a narrow space between the endothelium and the hepatic cells. Toward the periphery of the lobule, lymphatic capillaries appear which collect the lymph from these spaces and pass it on to the interlobular lymphatics. No lymph capillaries exist in the splenic pulp. In the brain, the cerebrospinal fluid seems to take over the functions of the lymph and thus renders unnecessary a complicated network of lymphatic capillaries.¹⁷⁹

The lymphatic vessels of the lower extremities pass into the femoral, inguinal, and iliac lymph nodes, thence by efferent vessels into the cisterna chyli. The *thoracic duct* arises from the cisterna and passes along the anterior part of the spine to enter the left subclavian vein near its junction with the left internal jugular vein. Lymph from the lower extremities, the intestinal tract and abdominal organs, the left upper extremity, and left side of the head drains into the cisterna chyli or the thoracic duct. The *right lymphatic duct* is only about 1.25 cm. in length. It enters the subclavian vein of the right side. Lymph from the right side of the head and neck, from the right upper extremity, and the right side of the trunk drains by various tributaries into this duct.¹⁷⁸

Collateral lymphatic channels open readily when a large lymph vessel is cut or obstructed. Regeneration of severed vessels occurs promptly. Reichert¹⁸⁰ observed new lymphatic vessels crossing a surgical scar on the fourth day, with physiologically complete regeneration by the eighth day.

Inflammations

Acute Lymphangitis.—This condition arises usually from small points of infection in the hands from contaminated slivers of wood, from infections acquired during postmortem examinations, from infection of feet from trimming a corn, or from a blister. The infecting organism is usually a streptococcus. Several lymph vessels draining the area become involved, together with the immediately adjacent tissue. As the infectious material passes up the arm toward the axillary lymph nodes, hyperemia and edema develop. Dusky red striae mark the course of the involved lymphatics, with edema and redness of the whole area. The walls of the lymphatics and the perilymphatic connective tissue are saturated with inflammatory exudate. The swollen lymph vessels are firm, tender, and cordlike, especially if coagulation (thrombosis) of lymph occurs. With prompt treatment a simple lymphangitis may disappear within four to fourteen days, the extremity remaining swollen after the exudate is absorbed. Regeneration of lymphatic endothelium occurs as healing progresses. In severe or neglected cases the process may become purulent. Purulent exudate bathes the wall and adjacent tissues, producing a phlegmonous inflammation. Abscesses are likely to form, thus complicating the picture. The process reaches the axillary or inguinal lymph nodes, resulting in buboes or actual abscesses which rupture and drain. If the lymph nodes are destroyed or the infection passes them, it enters the blood stream to initiate a septicemia.^{77, 181}

Chronic Lymphangitis.—In some instances the acute infection fails to heal due to neglect, to continuation of the infection due to the occupation of the patient, or for other reasons. Recurrent attacks of lymphangitis frequently cause a chronic form to develop. Chronic inflammation results with induration of the walls of the larger lymph vessels and adjacent soft tissue. Proliferation of the endothelial cells tends to obliterate the lumen. This is especially true of the smaller lymphatic vessels (productive lymphangitis).⁷⁷ Changes of this character interfere seriously with the absorptive capacity of the lymphatics.

Lymphedema

Although an important subject for the clinician, only a brief discussion is included here. Allen,¹⁸¹ who has studied 300 cases from the Mayo Clinic, classifies these under two headings: (1) *noninflammatory* and (2) *inflammatory*. The primary groups under (1) include *Lymphedema praecox* which develops in young females aged 9 to 25 years. Its onset is at puberty or in adolescence indicating an hormonal basis. *Congenital lymphedema*, another primary form, includes simple and hereditary types. Simple congenital lymphedema affects one member of a family, while the hereditary congenital type affects a number of blood relatives, indicating that the fault is due to a disturbance in the genes. This condition is known as "Milroy's disease," Milroy¹⁸² having described it originally in 1892. Many cases have been reported as Milroy's disease which do not conform to the

original description.¹⁸¹ The disease, as described by Milroy,¹⁸² is: (1) congenital (and familial); (2) the edema is limited to one or both lower extremities or portions thereof; (3) the edema is permanent, lasting throughout life; (4) there is an entire absence of constitutional or local symptoms. Furthermore, the disease appears not to shorten life.

In the simple form of congenital lymphedema, one extremity is swollen at birth or the parents notice the swelling a day or so afterward. The swelling progresses, the skin becomes roughened and often more or less pigmented over the swollen part. Examination of the cut surface of such tissues reveals a spongy translucent tissue of considerable width, lying between the skin and deep fascia. One-third to two-thirds of the fat is replaced by this spongy layer. If the living tissue is incised, a large quantity of clear fluid runs from the cut surfaces. On microscopic examination the outstanding feature is partial replacement of adipose tissue by enlarged lymph spaces, which are surrounded by rather loosely arranged connective tissue containing blood vessels. The spaces are lined by a single row of endothelial cells. The greater number of lymph spaces are found near the deep fascia. The microscopic appearance is characteristic for the congenital type. Allen suggests that the term "congenital lymphangiectasis" is more descriptive than congenital lymphedema.

Secondary lymphedema of the noninflammatory group is due to occlusion of lymphatic vessels by cells of malignant tumors of the breast, cervix uteri, uterus, prostate, and others. The lymphoblastomas may likewise be responsible for such blockage. Lymphedema may result from surgical removal of axillary lymphnodes for carcinoma of the breast. Its occurrence is irregular and often long periods of time intervene between the operation and swelling of the arm. Fibrosis and scarring may be enhanced by irradiation or by low-grade infection. Extensive removal of lymph nodes fails to produce edema in the experimental animal.¹⁸⁰

Lymphedema Due to Inflammation.—Chronic edema due to venous obstruction may predispose to recurrent attacks of cellulitis and lymphangitis, thus inducing a progressive lymphedema. (For discussion of acute and chronic lymphangitis, see above.) Trichophytosis of the toes may be responsible for recurrent attacks of lymphangitis. Systemic diseases such as influenza, typhoid, pneumonia, and malaria may lead to thrombophlebitis as a result of cellulitis and lymphangitis. If lymphatic obstruction occurs simultaneously, as demonstrated by Homans,¹⁸⁴ lymphedema results.¹⁸⁵

Lymphedema Due to Filariasis.—The kind of filariasis that causes lymphedema and elephantiasis in man is caused by the nematodes *Wuchereria bancrofti* and *W. Malayi*. See discussion on page 395.

References

Anatomy of Blood Vessels

- Maximov, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, 1942, W. B. Saunders Co.
- Cowdry, E. V.: The Structure and Physiology of Blood Vessels. Arteriosclerosis, New York, 1933, The Macmillan Co., pp. 53-76.

- Zweifach, B. W.: Anat. Rec. 73: 475, 1939.
- Chambers, R., and Zweifach, B. W.: Am. J. Anat. 75: 173, 1944.

Congenital Anomalies

- Symmers, D.: Status Lymphaticus, Am. J. M. Sc. 156: 40, 1918.
- Abbott, M. E.: (Statistics of Congenital Cardiac Disease—1,000 cases analyzed) Nelson's Loose Leaf Medicine IV, p. 229.
- Herbut, P. A.: Arch. Path. 35: 717, 1943.
- Taussig, Helen B.: Congenital Heart Disease, New York, 1947, The Commonwealth Fund.
- Abbott, M. E.: Congenital Heart Disease, Nelson's Looseleaf Medicine IX, p. 249.
- Hamilton, W. F., and Abbott, M. E.: Am. Heart J. 3: 381, 1927-1928.

Arteriosclerosis

- Page, I. H.: Arteriosclerosis and Lipid Metabolism, Biol. Symposia 11: 43, 1945.
- Wells, H. G.: Chemistry of Arteriosclerosis in Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Co., pp. 323-353.

Medial Calcification

- Blumenthal, H. T., Lansing, A. I., and Wheeler, P. A.: Am. J. Path. 20: 665, 1944.
- Stief, A., and Tokay, L.: J. Nerv. & Ment. Dis. 81: 633, 1935.
- Waterman, N.: Virchows Arch. f. path. Anat. 191: 202, 1908.
- Beneke, R.: München. med. Wchnschr. 66: 1463, 1919.
- Hueper, W. C.: Arch. Path. 38: 162, 1944.

Arteriolosclerosis

- Moritz, A. R., and Oldt, M. R.: Am. J. Path. 13: 679, 1937.
- Bell, E. T.: Textbook of Pathology, ed. 5, Philadelphia, 1944, Lea & Febiger.

Etiology of Arteriosclerosis

Adrenalin-type Scleroses

- Josue, M. O.: Cited by Hueper.²¹
- Hueper, W. C.: Arch. Path. 35: 846, 1943.
- Hueper, W. C.: Etiology and Morphology, Biol. Symposia 11: 1, 1945.
- Page, I. H.: Ann. Int. Med. 14: 1741, 1940-41.
- Klotz, O.: Experimental Arteriosclerosis: Proc. Second Congress International Soc. for Geog. Path. Utrecht, Holland, 1934.

Effects of Bacteria and Their Toxins

- Ophüls, W.: J. A. M. A. 76: 700, 1921.
- Duff, G. L.: Arch. Path. 13: 543, 1932.
- Klotz, O.: Brit. M. J. 2: 1767, 1906; and J. Path. & Bact. 16: 211, 1911-12.

Dietary Factors

- Ignatowski, A.: Virchows Arch. f. path. Anat. 198: 248, 1909.
- Anitschkow, N.: Experimental Arteriosclerosis in Animals, in Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Co., pp. 271-322.
- Anitschkow, N., and Chalatow, S.: Zentralbl. f. allg. path. u. path. Anat. 24: 1, 1913.
- Wacker, L., and Hueck, W.: München. med. Wchnschr. 60: 2097, 1913.
- McMeans, J. W., and Klotz, O.: J. Med. Res. 34: 41, 1916.
- Steiner, A., Kendall, F., and Evans, Margaret: Am. Heart J. 38: 34, 1949.
- Duff, G. L.: Arch. Path. 20: 81, 1935; and 22: 161, 1936.

Relation of Arteriosclerosis to Senescence

- Ophüls, W.: Pathogenesis of Arteriosclerosis, in Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Co., p. 249.
- Aschoff, L.: Introduction, in Cowdry, E. V.: Arteriosclerosis, New York, 1933, The Macmillan Co.

37. White, N. K., Edwards, J. E., and Dry, F. J.: *Circulation* **1**: 645, 1950.
 38. Wilens, S. L.: *Am. J. Path.* **13**: 811, 1937.
 39. Hass, G. M.: *Arch. Path.* **34**: 971, 1942; and **35**: 29, 1943.
 40. Ranke, O.: *Beitr. z. path. Anat. u. z. allg. Path.* **75**: 269, 1926.
 41. Oberndorfer: Quoted from Page,¹¹ p. 64.
 42. Hueper, W. C.: *Arch. Path.* **41**: 139, 1946.
 43. Dock, Wm.: *Bull. New York Acad. Med.* **26**: 182, 1950.

Imbibition Theory

44. Virchow, R.: Cited from Aschoff, L.: *Lectures in Pathology*, New York, 1924, Paul B. Hoeber, Inc., p. 131.
 45. Aschoff, L.: Cited from Gubner, R., and Ungerleider, H. E.: *Am. J. Med.* **6**: 60, 1949.

Theory of Leary and Klotz

46. Leary, T.: *Arch. Path.* **32**: 507, 1941.

Theory of Intramural Hemorrhage

47. Winternitz, M. C., Thomas, R. M., and Compte, P. M.: *Biology of Arteriosclerosis*, Springfield, Ill., 1938, Charles C Thomas.

Theory of Anoxemia

48. Hueper, W. C.: *Arch. Path.* **38**: 1944; and **39**: 1945.
 49. Page, I. H.: *Biol. Symposia* **11**: 43, 1945.

Atherosclerosis and Lipid Metabolism

50. Hirsch, E. F., and Weinhouse, S.: *Physiol. Rev.* **23**: 185, 1943.
 51. Steiner, A., and Domanski, B.: *Arch. Int. Med.* **71**: 397, 1943.
 52. Morrison, L. M., Hall, L., and Chaney, A. L.: *Am. J. M. Sc.* **216**: 32, 1948.
 53. Gertler, M. M., Garn, S. M., and Bland, E. F.: *Circulation* **2**: 517, 1950.
 54. Davidson, J. D., Liese, L. A., and Kendall, F. E.: *Am. Heart J.* **38**: 462, 1949.
 55. Kellner, H., Correll, J. W., and Ladd, A. F.: *Am. Heart J.* **38**: 460, 1949.
 56. Gofman, J. W., Jones, H. B., Lindgren, F., Lynn, T. P., Elliot, H. H., and Strisower, B.: *Circulation* **2**: 161, 1950.
 57. Lewis, Lena, and Page, I. H.: *Proc. Am. Soc. for Study of Arteriosclerosis*, *Circulation* **2**: 466, 1950.
 58. Turner, K. B., and Steiner, A.: *J. Clin. Investigation* **18**: 45, 1939.
 59. Keyes, A.: *Science* **122**: 79, 1950.
 60. White, P.: *Bull. New York Acad. Med.* **10**: 347, 1934.
 61. Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and van Slyke, D. D.: *J. Biol. Chem.* **111**: 613, 1935.
 62. Weinhouse, S., and Hirsch, E. F.: *Arch. Path.* **30**: 856, 1940.
 63. Steiner, Paul E.: *Arch. Path.* **42**: 359, 1946.
 64. Benjamin, E. L.: *U. S. Naval Medical Bull.* p. 495, 1946.
 65. Dale, Chas.: Personal communication.
 66. Virtanen, I., and Kanerva, K.: *Ann. Med. Int. Fenniae* **36**: 748, 1947.
 67. Thomas, W. A.: *J. A. M. A.* p. 1559, May 15, 1927.
 68. Eilert, Mary L.: *Mod. Concepts Cardiovascular Dis.* **20**: 92, 1951.

Heredity, Environment, and Constitutional Factors

69. Weitz, W.: Quoted by Williams, G. L., in Cowdry, E. V.: *Arteriosclerosis*, New York, 1933, The Macmillan Co., pp. 537-567.

*Inflammatory Lesions of the Arteries**Syphilitic Aortitis and Arteritis*

70. White, P. D.: *Heart Disease*, ed. 3, New York, 1944, The Macmillan Co.
 71. Clawson, B. J., and Bell, E. T.: *Arch. Path. & Lab. Med.* **4**: 922, 1927.
 72. Lippman: Cited by Kaufmann.⁷⁷
 73. Scott, R. W.: *Diseases of Aorta*, Oxford Medicine II, Pt. 2, p. 508(4).
 74. Derick, C. L., and Hass, G. M.: *Am. J. Path.* **11**: 291, 1935.
 75. Moritz, A. R.: *Arch. Path.* **11**: 44, 1931.

76. Heubner, O.: Quoted from Long, E. R.: *The Development of Our Knowledge of Arteriosclerosis*, in Cowdry, E. V.: *Arteriosclerosis*, New York, 1933, The Macmillan Co.
 77. Kaufmann, E.: *Pathology* (Translation by Reimann, I.), 129, Philadelphia, 1929, Blakiston's Son & Co.

Tuberculous Arteritis

78. Kayne, G. G., Pagel, W., and O'Shaughnessy, L.: *Pulmonary Tuberculosis*, New York, 1939, Oxford University Press.

Raynaud's Disease

79. Raynaud, M.: Quoted from Allen, Barker, and Hines,⁸²
 80. Hines, E. A., Jr., and Christensen, N. A.: *J. A. M. A.* **129**: 1, 1945.
 81. Allen, E. V.: *Proc. Staff Meet. Mayo Clin.* **12**: 187, 1937.
 82. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: *Peripheral Vascular Diseases*, Philadelphia, 1946, W. B. Saunders Co.

Scleroderma

83. Brown, G. E., O'Leary, P. A., and Adson, A. W.: *Ann. Int. Med.* **4**: 531, 1930-31.
 84. Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T.: *Arch. Int. Med.* **71**: 749, 1943.

Arteriosclerosis Obliterans

85. Sappington, S. W., and Fisher, H. R.: *Arch. Path.* **34**: 989, 1942.

Diabetic Gangrene

86. Warren, Shields: *The Pathology of Diabetes Mellitus*, Philadelphia, 1939, Lea & Febiger.
 87. Hines, E. A., Jr., and Barker, N. W.: *Am. J. M. Sc.* **200**: 717, 1940.

Thrombo-angiitis Obliterans (Buerger's Disease)

88. Samuels, S. S.: *Am. J. M. Sc.* **183**: 465, 1932.
 89. Silbert, Samuel: *J. A. M. A.* **89**: 964, 1927, and **102**: 11, 1934.
 90. Buerger, Leo: *Surg., Gynec. & Obst.* **19**: 582, 1914.
 91. Buerger, Leo: *The Circulatory Disturbances of the Extremities; Including Gangrene, Vasomotor and Trophic Disorders*, Philadelphia, 1924, W. B. Saunders Co.

Periarteritis Nodosa

92. Harris, W. A., Lynch, G. W., and O'Hare, J. P.: *Arch. Int. Med.* **63**: 1163, 1939.
 93. Logue, R. B., and Mullins, F.: *Ann. Int. Med.* **24**: 11, 1946.
 94. Rich, A. R.: *Bull. Johns Hopkins Hosp.* **71**: 123, 1942.
 95. Banks, B. M.: *New England J. Med.* **225**: 433, 1941.
 96. Arkin, Aaron: *Am. J. Path.* **6**: 401, 1930.
 97. Krupp, Marcus: *Arch. Int. Med.* **71**: 54, 1943.

Temporal Arteritis and Giant-Ceiled Arteritis

98. Horton, B. T., Magath, T. B., and Brown, G. E.: *Proc. Staff Meet. Mayo Clin.* **7**: 700, 1932.
 99. Johnson, R. H., Harley, R. D., and Horton, B. T.: *Am. J. Ophthalm.* **26**: 147, 1943.
 100. Harrison, C. V.: *J. Clin. Path.* **1**: 197, 1948.
 101. Hutchinson, J.: *Arch. Surg.* **1**: 323, 1890 (London).

Disseminated Lupus Erythematosus

102. Klemperer, P., Pollack, A. D., and Baehr, G.: *Arch. Path.* **32**: 569, 1941; *J. A. M. A.* **119**: 331, 1942.
 103. Klemperer, P.: *Am. J. Path.* **26**: 505, 1950.

Malignant Nephrosclerosis

104. Klemperer, P., and Otani, S.: *Arch. Path.* **11**: 60, 1931.

Aneurysms

- Etiology
 105. Kampmeier, R. H.: *Ann. Int. Med.* **12**: 624, 1938-39.

Pathologic Anatomy

106. Karsner, H. T.: Human Pathology, ed. 6, Philadelphia, 1942, J. B. Lippincott Co.
 107. Boyd, L. J.: Am. J. M. Sc. **168**: 654, 1924.

Visceral Aneurysms

108. Machemer, W. L., and Fuge, W. W.: Arch. Surg. **39**: 190, 1939.
 109. McNealy, R. W.: Aneurysms, in Lewis, D.: Practice of Surgery, Hagerstown, Md., 1944, W. F. Prior Co., XII, Chap. V.E, p. 69.

Aneurysm of Pulmonary Trunk

110. Boyd, L. J., and McGavack, T. H.: Aneurysm of the Trunk and Main Branches of the Pulmonary Artery: Analysis of 152 cases, Modern Concepts of Cardiovascular Disease, X, New York, February, 1941, American Heart Association.

Dissecting Aneurysm of the Aorta

111. Rogers, H.: Dissecting Aneurysm of the Aorta, Modern Concepts of Cardiovascular Disease IX, New York, April, 1940, American Heart Association.
 112. Amromin, George D., Schlichter, J. G., and Solway, A. J. L.: Arch. Path. **46**: 380, 1948.
 113. Klotz, O., and Simpson, W.: Am. J. M. Sc. **184**: 455, 1932.
 114. Moritz, A. R.: Am. J. Path. **8**: 717, 1932.
 115. Gsell, O.: (Quoted by Sailer¹¹⁹) Virchows Arch. f. path. Anat. **270**: 1, 1928.
 116. Erdheim, J.: Virchows Arch. f. path. Anat. **273**: 454, 1929.
 117. Erdheim, J.: Virchows Arch. f. path. Anat. **276**: 187, 1930.
 118. Rottino, A.: Arch. Path. **28**: 1 and 377, 1939.
 119. Sailer, S.: Arch. Path. **33**: 704, 1942.
 120. Duff, G. L.: Arch. Path. **18**: 543, 1932.
 121. Hueper, W. C.: Etiology and Morphology of Arteriosclerosis, Biol. Symposia **11**: 1, 1945.
 122. Rindfuss, E.: (Quoted by Sailer¹¹⁹) Virchows Arch. f. path. Anat. **96**: 302, 1884; and **131**: 374, 1893.
 123. Hall, E. M.: Arch. Path. & Lab. Med. **2**: 41, 1926.
 124. Flaxman, N.: Am. Heart J. **24**: 654, 1942.

Miliary Aneurysm of the Cerebral Arteries

125. Forbus, W. D.: Bull. Johns Hopkins Hosp. **47**: 239, 1930.
 126. Turnbull, H. M.: Quart. J. Med. **8**: 201, 1914-15.
 127. Glynn, L. E.: J. Path. & Bact. **51**: 213, 1940.
 128. Dandy, W. E.: Vascular Lesions of Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., 1944, W. F. Prior Co., Sec. XII, Chapt. 1, pp. 398 and 399.
 129. Courville, C. B., and Olsen, C. W.: Bull. Los Angeles Neurol. Soc. **3**: 1, 1938.

Embolic and Mycotic Aneurysms

130. Osler, W. (Cited by Stengel and Wolferth¹³²): Brit. M. J. **1**: 467, 1885.
 131. Eppinger (Cited by Stengel and Wolferth¹³²): Arch. f. klin. Chir. **35**: 1887.

Erosive Aneurysms

132. Stengel, A., and Wolferth, C. C.: Arch. Int. Med. **31**: 527, 1923.

Arteriovenous Aneurysm

133. Rienhoff, W. F., Jr.: Bull. Johns Hopkins Hosp. **35**: 271, 1924.

Cirsoid Aneurysms

134. Wagner: Quoted from Lewis, D.: Practice of Surgery, Hagerstown, Md., 1944, W. F. Prior Co., XII, Chap. V.E, p. 54.

*Diseases of the Veins**Congenital Malformation*

135. Dandy, W. E.: The Brain, in Lewis, D.: Practice of Surgery, Hagerstown, Md., 1944, W. F. Prior Co., XII, Chap. 1.

Acute and Chronic Phlebitis

136. Hueper, W. C.: Am. J. Clin. Path. **16**: 207, 1946.

Phlebosclerosis

137. Lobstein: Quoted by Hauswirth and Eisenberg.¹³³
 138. Hauswirth, L., and Eisenberg, A. A.: Arch. Path. **11**: 857, 1931.
 139. Martin, C. F., and Meakins, J. C.: Am. Med. **10**: 611, 1905.
 140. Levin, P. M., and Bucy, P. C.: Arch. Int. Med. **57**: 787, 1936.

Tuberculosis

141. Kayne, G. G., Pagel, W., and O'Shaugnessy, L.: Pulmonary Tuberculosis, New York, 1939, Oxford University Press.

Phlebothrombosis and Thrombophlebitis

142. Ochsner, Alton, De Bakey, M. D., De Camp, P. T., and de Rocha, E.: Surgery **29**: 24, 1951; Ann. Surg., Sept., 1951.
 143. Quick, A. J.: Surg., Gynec. & Obst. **91**: 296, 1950.
 144. Ware, A. G.: M. Bull. Univ. S. Calif. **2**: 20, 1950.
 145. Welch, W. H.: Trans. Path. Soc. Phil. **13**: 281, 1887.
 146. Hadfield, Geoffrey: Ann. Royal Coll. Surgeons England **6**: 219, 1950.
 147. Tocantins, L. M.: Medicine **17**: 155, 1938.
 148. McLachlin, John, and Paterson, J. C.: Surg., Gynec. & Obst. **93**: 1, 1951.
 149. Moolten, S. E., Vroman, L., Vroman, G. M. S., and Goodman, B.: Arch. Int. Med. **84**: 667, 1949.
 150. Rössle, R.: Virchows Arch. f. path. Anat. **300**: 180, 1937.
 151. Dock, W.: Conferences on Therapy, New York State J. Med. **44**: 724, 1944.
 152. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Arch. Int. Med. **68**: 1, 1941.
 153. Neumann, R.: Virchows Arch. f. path. Anat. **301**: 708, 1938.
 154. Homans, J.: Am. Heart J. **7**: 415, 1932.

Thrombosis of Superior and Inferior Vena Cava

155. Ochsner, O., and Dixon, J. L.: J. Thoracic Surg. **5**: 641, 1935-36.
 156. Blumer, G.: Thrombosis of the Inferior Vena Cava, in Osler, W.: Modern Medicine, Philadelphia, 1907, Lea & Febiger, Vol. 4, p. 529.

Thrombosis of Portal Veins

157. Lissauer: Quoted from Simonds.¹⁵⁹
 158. Pick: Quoted from Simonds.¹⁵⁹
 159. Simonds, J. P.: Arch. Surg. **33**: 397, 1936.

Thrombosis of Hepatic Veins (Chiari's Disease)

160. Chiari, H.: Beitr. z. path. Anat. u. z. allg. Path. **26**: 1, 1899.
 161. Hirsh, H. L., and Manchester, B.: New England J. Med. **235**: 507, 1946.
 162. Armstrong, C. D., and Carnes, W. H.: Am. J. M. Sc. **208**: 470, 1944.

Varicose Veins

163. Ochsner, A.: Varicosities of the Lower Extremity, in Lewis, D.: Practice of Surgery, Baltimore, Md., 1944, W. F. Prior Co., XII, Chap. V.A.
 164. Larson, R. A., and Smith, F. L.: Proc. Staff Meet., Mayo Clin. **18**: 400, 1943.
 165. Rutledge, D. I.: Quoted by Allen, Barker, and Hines.³²
 166. Ochsner, A., and Mahorner, H. R.: Varicose Veins, St. Louis, 1939, The C. V. Mosby Co.
 167. Pratt, G. H.: Am. J. Surg. **44**: 31, 1939.

Tumors of Blood and Lymphatic Vessels

168. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Co.
 169. Ribbert, V. A.: Virchows Arch. f. path. Anat. **151**: 381, 1898 (hemangioma).
 170. Bucy, P. C., and Capp, C. S.: Am. J. Roentgenol. **23**: 1, 1930 (hemangioma).
 171. von Hippel, E.: Arch. f. Ophth. **59**: 83, 1904 (Lindau's [von Hippel's] Disease).
 172. Lindau, A.: Quoted by Noran.¹⁷³
 173. Noran, H. H.: General Review—Intracranial Vascular Tumors and Malformations. Arch. Path. **39**: 293, 1945.

174. Shuck, I. D.: Quoted by Ewing¹⁸⁸ (racemose hemangioma).
175. Hall, E. M.: Am. J. Path. **11**: 343, 1935 (metastasizing hemangioma).
176. Wegner, G.: Quoted by Allen, Barker and Hines⁶² (lymphatic vessels).
177. Goetsch, E.: Arch. Surg. **36**: 394, 1938 (hygroma colli cysticum).
- Diseases of Lymphatic Vessels*
- Anatomy*
178. Gray, H.: Human Anatomy, edited by W. H. Lewis (ed. 23), Philadelphia, 1936, Lea & Febiger.
179. Drinker, C. K., and Yoffey, J. M.: Lymphatics, Lymph and Lymphoid Tissue, Cambridge, Mass., 1941, Harvard University Press.
180. Reichert, F. L.: Arch. Surg. **13**: 871, 1926.
- Lymphangitis*
181. Allen, E. V.: Arch. Int. Med. **54**: 606, 1934.
- Lymphedema (Obstructive Lesions)*
182. Milroy, W. F.: New York Med. J. **56**: 505, 1892.
183. Milroy, W. F.: J. A. M. A. **91**: 1172, 1928.
184. Homans, John: Ann. Surg. **87**: 641, 1928.
185. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Disease, Philadelphia, 1946, W. B. Saunders Co.

Chapter 21

THE KIDNEYS

W. A. D. ANDERSON

Renal Structure and Function

The kidneys are composed of units (nephrons), each consisting of a glomerulus and its associated tubule. A normal human kidney contains about 1.25 million nephrons, sufficient for a considerable reserve. The glomerulus is a collection of capillaries covered by epithelium continuous with that lining the tubule. A thin basement membrane separates the epithelial covering of the glomerular capillaries from the endothelial lining. The total surface of a glomerular tuft is very large, and their aggregate surface is enormous. The glomerulus acts as a filter, and from blood flowing through its capillaries a protein-free filtrate of the plasma collects in the glomerular space and flows down the tubule. During this tubular passage there is active resorption of water, glucose, chloride, sodium, and other substances. It is possible that there also is active secretion by tubules of certain substances, notably creatinine and ammonia. For this mechanism to function normally in the nephron there must be (1) a free flow of blood through the capillaries of the tuft; (2) a normal filter, i.e., water, salt, urea, and other waste products must be allowed to filter through, but certain substances such as plasma proteins held back; (3) a normal epithelial lining of the tubule and an unblocked lumen. Lesions in the kidney can produce functional disturbance by three corresponding types of qualitative change. Each may occur alone, but combinations of varying degrees of each are the usual occurrence. The large numerical reserve of identical units is such that a fraction of their number can maintain adequate function. Consequently, functional changes in relation to renal lesions must be considered on a quantitative as well as a qualitative basis. When functional deficiency occurs in chronic glomerulonephritis and nephrosclerosis, values for urea and creatinine clearance are closely correlated with the number of functioning glomeruli.

The vessels of the glomerular tuft, after forming the efferent arteriole, again break up into capillaries which supply the tubule. Hence, obstruction of flow through the glomerulus also interferes with tubular blood supply. Destruction of a glomerulus usually results in atrophy and disappearance of the corresponding tubule, although aglomerular tubules have been demonstrated. Glomeruli do not regenerate. No new glomeruli are formed during adult life, though some compensation may result from hypertrophy of those remaining. Tubular epithelium, on the other hand, regenerates readily. Hence, injurious agents which affect the tubular epithelium alone, e.g., mercury bichloride, lead

either to death of the individual or to complete recovery, i.e., the injury is neither chronic nor progressive. Following injury, regenerated tubular epithelial cells may have an atypical flattened form and are more resistant to injury.

The presence of alkaline phosphatase may be demonstrated in renal tissue by a specific histochemical stain. The enzyme probably has a role in tubular reabsorption of sugar by dephosphorylating hexose phosphates. Decrease of phosphatase is found when there is disturbance of tubular function, as in hydronephrosis.

Classification of Renal Diseases

Cardiovascular renal disease is a term used broadly to include the vascular and inflammatory disorders of the kidneys, associated vascular lesions of other organs, and the effects on the heart and brain. Including, as it does, most conditions accompanied by high blood pressure, this group of disorders causes about one-third of all deaths and is the cause of one-half of all deaths past the age of 50 years. Little is known about etiology, prevention, or effective treatment in most of these conditions. Although the kidneys play an essential part in these disorders, the underlying renal lesions may be of different types. Renal diseases of different origin and nature may produce essentially similar disturbances of renal function, and hence may have much clinical similarity. Also, renal disturbances of different pathogenesis may reach late or end stages which are morphologically similar, and hence not always easy to differentiate.

No single method of classification of renal diseases is easily applicable, and the method used herein is based on a combined consideration of the portion of the kidney primarily or most prominently affected and the type of involvement. While certain parts of the renal structure, such as glomeruli, tubules, blood vessels, or interstitial tissue, appear to be primarily or mainly involved in any given case, and hence allow a certain classification of the disease, it should be recognized

that the other parts of the kidney almost always show some secondary or less prominent pathologic change.

1. Glomerular disease: glomerulonephritis
 - diffuse—acute
 - subacute
 - chronic
 - focal
2. Vascular disease: nephrosclerosis
 - atherosclerotic
 - arteriolosclerotic
 - periarteritis nodosa
 - bilateral cortical necrosis
 - diabetic glomerulosclerosis
 - infarcts of the kidney
 - orthostatic albuminuria
3. Tubular disease—nephrosis or tubular nephritis:
 - lipoid nephrosis
 - toxic nephrosis
 - chemical nephrosis
4. Interstitial disease:—interstitial nephritis
 - acute diffuse
 - chronic diffuse
 - focal suppurative
 - pyelonephritis
 - syphilis
 - tuberculosis
 - leukemic infiltration
5. Obstructive disease of the kidney:—hydro-nephrosis
6. Metabolic renal disease:
 - hyperparathyroid renal disease
 - hypervitaminosis D
 - renal calculi
 - uric acid infarcts
 - renal lesions in gout
7. Congenital malformation and anomalies:
 - agenesis
 - hypoplasia
 - fusion
 - ectopia
 - cysts
8. Tumors:
 - benign
 - hamartoma
 - adenoma
 - fibroma
 - leiomyoma
 - lipoma
 - malignant—hypernephroma and carcinoma
 - Wilms' tumor (adenomysarcoma)
 - carcinoma of the pelvis
 - metastatic

Glomerulonephritis

In glomerulonephritis the lesion is primarily an inflammation affecting glomerular tufts, with secondary changes in tubules, interstitial tissue, and blood vessels. The inflammatory reaction in the glomerular tufts is manifested by (a) proliferation and swelling of capillary endothelium, (b) proliferation of capsular and glomerular tuft epithelium, (c)

thickening of basement membranes, (d) formation of intracapillary fibers, and (e) exudation of leukocytes, serum, and fibrin. In most cases proliferative manifestations are predominant. Some exudation occasionally is associated, and sometimes exudation of leukocytes is a prominent feature. The change is usually quite diffuse, affecting most of the glomeruli but with variable degrees of severity. Focal forms of glomerulonephritis also occur, however, mainly as a result of embolic phenomena.

The effect of the inflammatory changes in the glomeruli is to narrow or obliterate the capillaries of the glomerular tufts. This obstruction to the passage of blood through the glomerular capillaries interferes with the formation of the glomerular filtrate, in addition to effect from injury to the filter itself. The blood supply of the tubules also is affected by the glomerular capillary obstruction. If the condition progresses, the glomerular tufts gradually become hyalinized, and many may completely disappear. The corresponding tubules also atrophy, although rare aglomerular tubules have been shown to persist. The atrophy and disappearance of nephrons results in shrinkage of renal substance, with condensation of interstitial connective tissue as well as some absolute increase in connective tissue. The tubules associated with glomeruli which remain permeable and functioning, at least partly, tend to undergo hypertrophy. A variety of secondary degenerative changes are found in the tubules. In prolonged chronic cases secondary sclerotic changes are found in small arteries and arterioles, and in late stages with marked hypertension the arteriolar sclerosis may be severe and may have an important role in accelerating the fatal ending.

Diffuse glomerulonephritis may be subdivided into acute, subacute, and chronic forms or stages. There is no very definite or clear-cut line of division between these various forms, and borderline instances occur in which arbitrary division is necessary. The acute form is more common in children, lasts only a few weeks, and may entirely clear up, may cause death, or may progress to subacute or chronic forms. The subacute form lasts several

months to a year, and the chronic form may be present over many years, often with long periods of clinical latency. The subacute and chronic forms may not be preceded by a clinically recognized acute phase. Chronic forms sometimes

of renal function, the final stage presenting a condition referred to as uremia.

Incidence and Etiology.—Glomerulonephritis is estimated to cause less than 1 per cent of deaths in the United States. This does not, of course, give a true picture of the incidence because many patients with acute glomeruloneph-

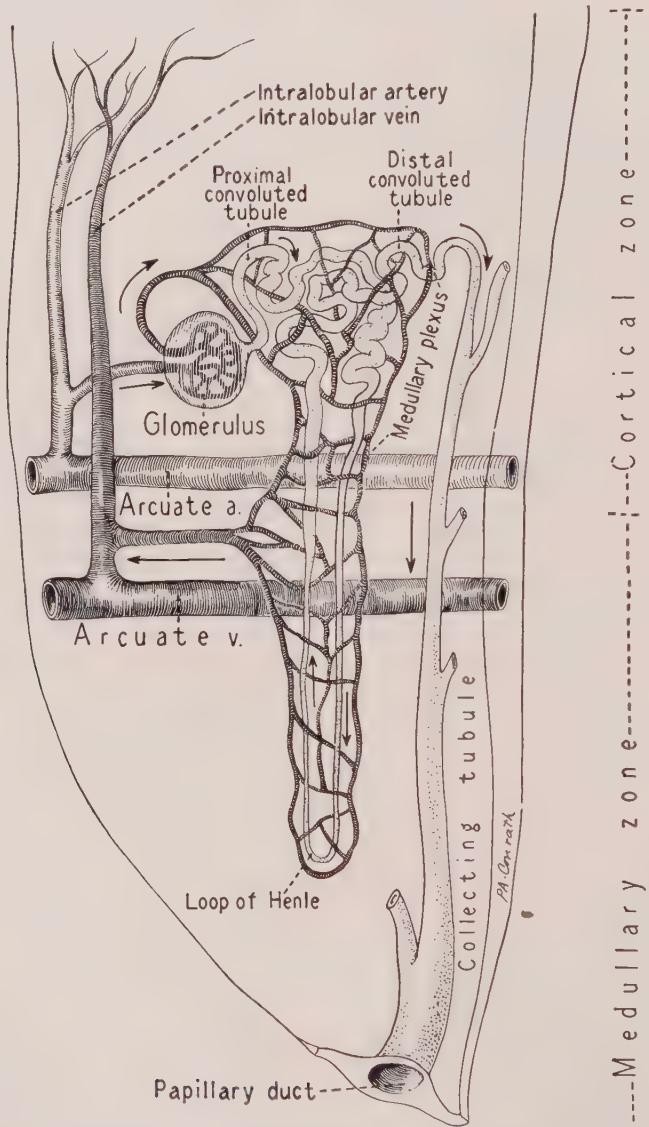


Fig. 432.—Nephron. Diagrammatic representation of a renal unit, showing circulatory relationships.

show intermittent periods of acute exacerbation interspersed with latent periods of low or subclinical activity. The subacute and chronic forms, unlike many acute cases, do not subside and disappear, but usually relentlessly progress to failure

ritis recover, and probably many cases are mild and pass unrecognized. While glomerulonephritis may occur at any time of life, the great majority of cases are before the age of 40 years, and the highest incidence is in the first and second decades. The incidence in males appears to be about twice that in females,

although in some series of cases this sexual predilection has not been evident.

The full story of the etiology of diffuse glomerulonephritis is not yet known. The acute form of glomerulonephritis appears very frequently to follow an infection, particularly infection by a hemolytic streptococcus. In many cases the renal disease closely follows scarlet fever, sore throat, tonsillitis, or some other infection, but the proportion of such infections which is followed by nephritis is extremely small. While the relationship to infection appears well established, other factors which determine whether or not the infection will result in glomerulonephritis, and the mechanism of the renal injury are not known. Bacteria are ordinarily not demonstrable in the inflammatory renal lesions. That it is an allergic type of reaction of renal tissue to bacteria or their products has been suggested. The interval between the height of the infection and the appearance of glomerulonephritis, which in some infections such as scarlet fever may be two or three weeks, has been interpreted as favoring this hypothesis of allergy. Exacerbation of glomerulonephritis following repeated upper respiratory infections also has been looked upon as due to sensitization. Alternate hypotheses have been that the glomerular injury is produced by some bacterial toxin carried to the kidney by the blood stream, or by a specific strain of streptococci with particular potentiality for glomerular injury.

Studies of renal disease in experimental animals have been helpful only to a limited degree. Diffuse glomerulonephritis entirely comparable to human glomerulonephritis has not been observed to occur spontaneously in laboratory animals, and experimental reproduction has not been easily achieved. The closest approach in experimental reproduction appears to be the so-called "nephrotoxic nephritis." This is produced by injection of an emulsion of renal tissue from one species (e.g., rabbit) into another species (e.g., duck). Serum from the latter sensitized animals (anti-rabbit-kidney duck serum) when injected into the original species (rabbit) results in glomerular lesions in which epithelial proliferation and crescent formation may be prominent.

ACUTE DIFFUSE GLOMERULONEPHRITIS

Acute glomerulonephritis more clearly than any other stage of glomerulonephritis appears to be related to an infection which precedes its onset by a few days to two or three weeks. It occurs especially in the first two decades of life, and is characterized by proteinuria, casts and red blood cells in the urine, and sometimes by edema, impaired renal function, and hypertension. There is usually a definite oliguria.

The protein in the urine is predominantly albumin and is abundant, but the amount alone appears to be without reliable prognostic signifi-

cance. However, studies by Blackman and associates have indicated that a high total proteinuria in which the proportion of globulin is greater than usual is associated with greater accumulation of fibrin, hyaline, and organized exudate in the glomeruli, and with a relatively poorer prognosis. Casts found in acute nephritis are largely formed of precipitated albumin and have about the same significance as the proteinuria. The number of red cells in the urine is variable, but sometimes from ruptured glomerular capillaries they are sufficiently abundant to

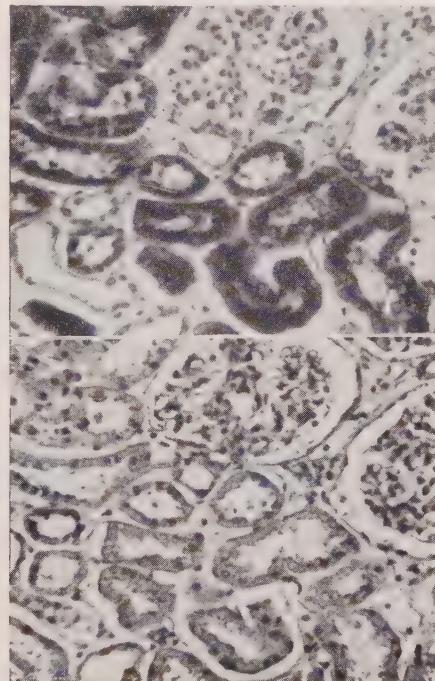


Fig. 433.—Phosphatase in kidney. Black areas (upper) indicate sites of phosphatase in tubular epithelium, with control stain of same area (lower).

cause gross hematuria. Edema in acute glomerulonephritis may vary from slight to marked degree, and its mechanism is not always easily explained. In some cases it is due to low plasma proteins as a result of albuminuria, and in other cases it appears to be caused by an associated cardiac decompensation. Hypertension when present in acute glomerulonephritis is usually of moderate degree.

A case of acute glomerulonephritis may end in one of several ways. A fatal outcome is usually due to renal functional insufficiency (uremia), but rarely may result from edema of the larynx or lungs. A large proportion of cases appear to clear up completely, leaving no serious residual renal damage. Some cases progress to subacute or chronic phases without subsidence of clinical evidences of activity of the disease, while others pass through a clinically latent period interrupted by recurrent exacerbations of activity or the gradual appearance of evidences of chronic glomerulonephritis.

Pathologic Anatomy.—In acute glomerulonephritis the kidneys are large, and the tense capsule strips easily from the markedly swollen renal substance. The outer surface is smooth and reddish, or pale with tiny reddish dots or minute hemorrhages. The cut surface shows a bulging, thickened, moist, cloudy cortex, which is pale in contrast to the congested and reddened pyramids.

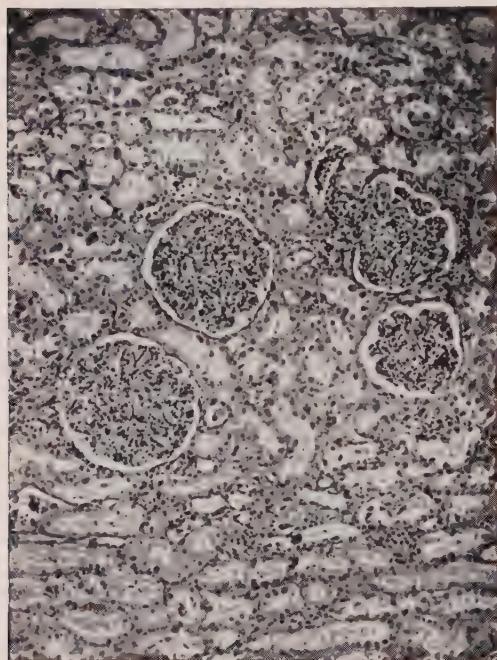


Fig. 434.—Acute glomerulonephritis. Note the large size and marked cellularity of the glomeruli.

Microscopically, the glomeruli appear enlarged, bloodless, and excessively cellular. This apparent increase of nuclei is mainly the result of endothelial proliferation, but leukocytes are sometimes numerous. The swelling and proliferation of capillary endothelial cells tend to block their lumina. Small hyaline intracapillary fibers are demonstrable by an azocarmine stain. They increase in size and number, eventually resembling collagen fibers. Occasionally, capillary thrombi are present. Proliferation of epithelial cells of the glomerular tuft may be present but is usually less conspicuous than endothelial proliferation. Some capsular proliferation may be present, the proliferated epithelial cells of the capsular lining forming crescent-shaped masses

which compress the glomerular tuft. Adhesions may form between the tuft and capsule. Tubules show varying degenerative changes, including fatty changes and sometimes hyaline droplet accumulation. The interstitial tissue is edematous, and may show some infiltration by leukocytes. The glomerular changes are usually diffuse, although not all glomeruli appear affected to an equal degree.

Glomerulitis.—In cases of death from a variety of infectious diseases, but particularly in bacterial endocarditis, rheumatic fever, tuberculosis and puerperal infection, glomerular lesions may be found. These changes may be swelling and proliferation of capillary endothelial cells of the glomerular tufts, occasionally with exudation of a few leukocytes. When of marked degree, the glomerular changes may simulate those of acute glomerulonephritis, but clinical manifestations of acute diffuse glomerulonephritis are lacking.

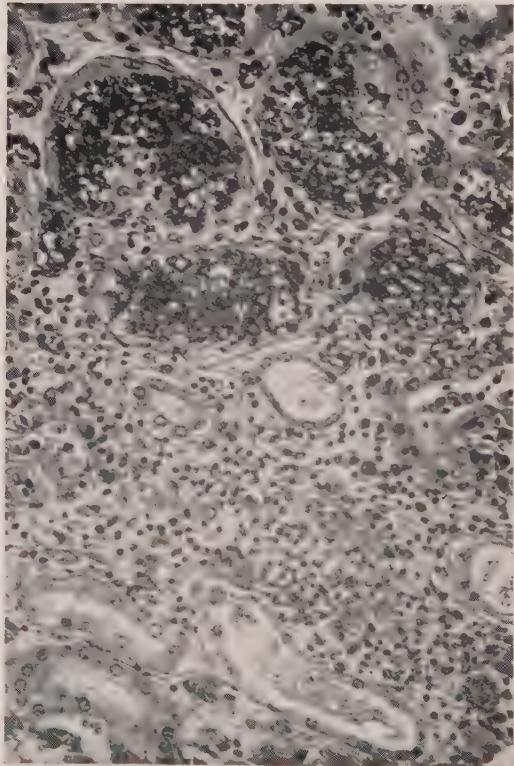


Fig. 435.—Acute hemorrhagic nephritis. Note the exudate and the tubular lumina filled with erythrocytes.

SUBACUTE GLOMERULONEPHRITIS

Glomerulonephritis terminating in uremia in the course of a few months is usually referred to as subacute. It may be

gin as a typical acute glomerulonephritis which is prolonged, or it may be a less severe type of inflammation from the beginning. Albuminuria is often abundant and edema severe. The massive albuminuria, low plasma proteins, marked edema, and elevated cholesterol may result in clinical confusion with lipoid

pale and soft, and have been referred to in the older literature as "large white kidneys" and "diffuse parenchymatous nephritis." There may be some slight irregularity of the surface of the kidney and some adherence of the capsule. The cut surface of the thick cortex appears cloudy and pale. The microscopic changes

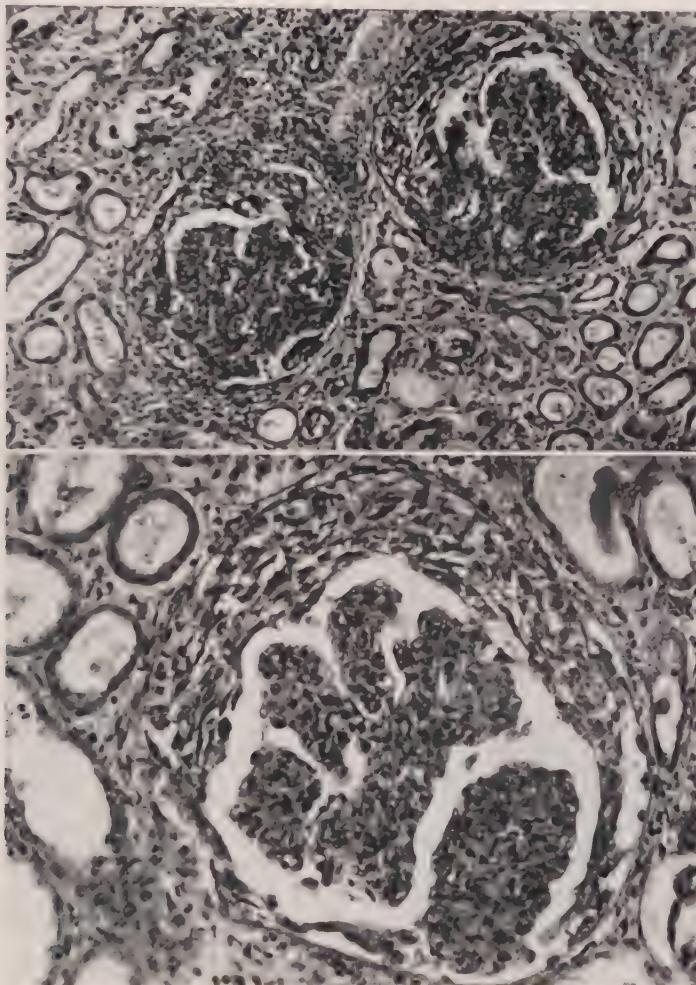


Fig. 436.—Subacute glomerulonephritis. Very marked proliferation and crescent formation are evident in addition to some exudation and tubular degeneration.

nephrosis (see page 575). However, unlike lipoid nephrosis, the blood pressure is usually increased (sometimes markedly), evidence of renal functional deficiency is present and progresses, and death is usually from uremia.

Pathologic Anatomy.—The kidneys in subacute glomerulonephritis are enlarged,

are severe, and usually show a fairly uniform involvement of all glomeruli. Epithelial proliferation is often prominent, and capsular "crescents" due to proliferation of capsular epithelium are frequently numerous and striking in appearance. Adhesions of tuft to capsule and obliteration of the capsular space are common.

Endothelial proliferation may be present in many glomerular tufts. Hyalinized glomeruli are absent or infrequent, but occasional fibrous crescents may be found. Tubular degenerative changes and tubular atrophy of marked degree are usually diffusely present. Many tubules contain casts. Interstitial connective tissue may appear slightly increased, but leukocytic exudation is absent or slight. The diffuseness and severity of the progressive

diffuse glomerulonephritis which progresses to a chronic phase. In such cases the history may be one of infection, an acute attack of nephritis, progression to a chronic phase without any latent period of apparent recovery, and termination with uremia. More frequently there is no history of an acute attack, because acute phases were mild and passed unnoticed. The condition may progress over many years, with little clinical evi-



Fig. 437.—Chronic glomerulonephritis. Note the granularity of the outer surface and the irregular narrowing of the cortex.
(Courtesy Dr. H. C. Schmeisser.)

proliferative and degenerative changes result in death from renal functional failure before much scarring or contraction of the kidneys develops. Blood vessels show slight or no changes.

CHRONIC GLOMERULONEPHRITIS

Chronic glomerulonephritis usually terminates in death from failure of renal function. It may result from an acute

dence except a slowly progressive decrease of renal function. In other cases there are long latent periods of apparent health, punctuated by mild acute flare-ups. The end result in each case is similar, with failure of renal function terminating in uremia.

The failure of renal function is manifested by decreasing ability to concentrate the urine, until there is a fixed specific gravity near 1.010,

corresponding to that of blood plasma. The dilute urine is excreted in large amount, resulting in polyuria and nocturia. Albumin and casts are present in the urine, but in small or moderate amounts. High blood pressure develops and increases with the progression of renal failure. Failure to excrete nitrogenous waste products is reflected in an increase of non-protein nitrogen and urea in the blood. The term "azotemic" nephritis is often used to refer to this form of nephritis which is characterized by elevation of blood urea. Edema is absent or slight, but may become more conspicuous with acute exacerbations. Secondary anemia occurs rather constantly, and may be severe in late stages. Termination occurs with the clinical syndrome known as uremia.

completely normal. Medium-sized and small arteries commonly develop intimal and medial proliferation and thickening. Renal ischemia due to the glomerular and vascular changes results in the hypertension of chronic nephritis. In some cases the gross and microscopic changes of chronic glomerulonephritis are not readily distinguishable from those of the primarily vascular condition, hypertensive nephrosclerosis.

The type and severity of the vascular changes in chronic glomerulonephritis

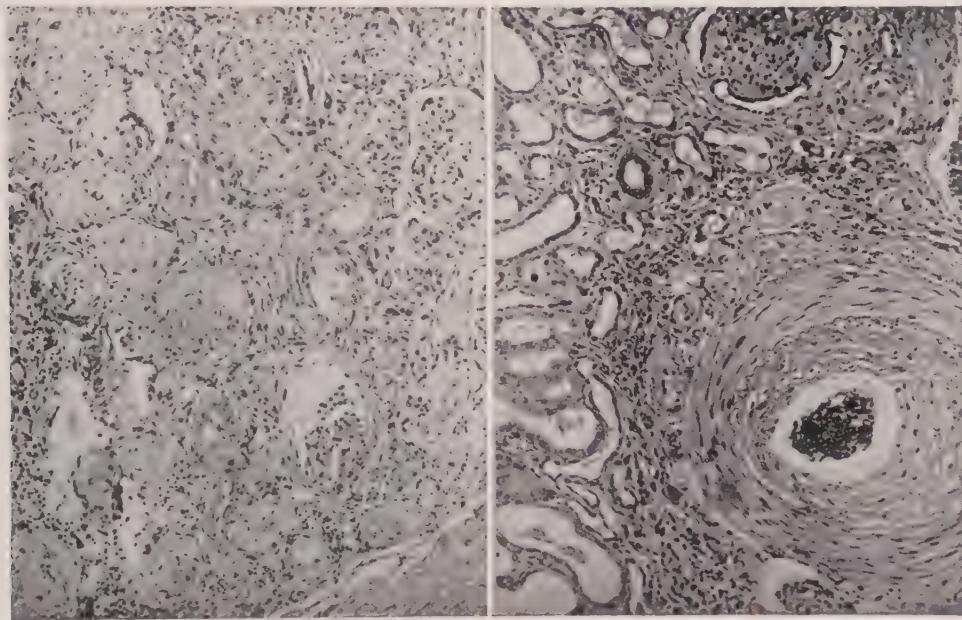


Fig. 438.—Chronic nephritis. Note the glomerular capsular adhesions and hyalinization, and thickening of blood vessels.

Pathologic Anatomy.—The kidneys are small, contracted, and firm. Their capsules are tightly adherent, and the outer surfaces are roughly and irregularly granular and pitted. The cortices are irregularly narrowed and scarred, with loss of normal architectural markings. Microscopically, a large proportion of glomeruli are partially or completely changed into hyaline masses. Many tubules are atrophic or have disappeared, and the amount of connective tissue between the tubules and glomeruli shows a great relative increase. Some tubules and glomeruli are permeable and apparently functioning, though none may be

have been shown to be correlated with the rate of progression of the disease. In slowly progressive cases, the vascular changes of intimal fibrosis, splitting and reduplication of elastic lamellae, and arteriolar hyalinization may be found. More severe vascular changes, particularly marked cellular intimal proliferation and arteriolar necrosis, are associated with accelerated progress of the disease in late stages. Such cases clinically may simulate "malignant hypertension" (see page 567), with very high blood pressures and retinal lesions.

Uremia.—Uremia is the complex clinical condition marking the final stage of

renal insufficiency. No particular substance or "toxin" is known to be causative, but it is probably an autointoxication due to retention of various metabolic products ordinarily eliminated by the urinary mechanism.

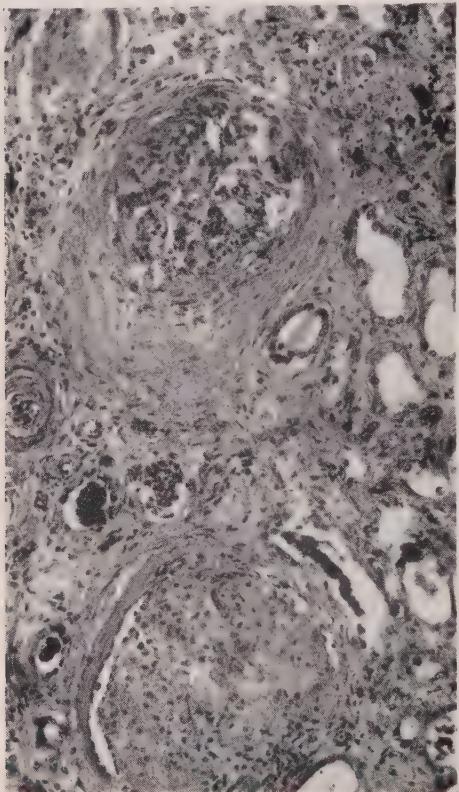


Fig. 439.—Chronic glomerulonephritis, terminal stage. Note the glomerular fibrosis, tubular dilatation, and arterial thickening. (Courtesy Dr. F. D. Murphy.)

Failure of function is denoted by inability of the kidneys to produce a concentrated urine and to adapt to increased work. In final stages of failure the specific gravity of the urine tends to be fixed about 1.010, the urine being practically isotonic with serum. Urea, creatinine, uric acid, sulfate, chloride, ammonia, and phosphate are retained. The hydrogen-ion concentration of the urine can no longer be varied to suit the body's need, and there is frequently a retention acidosis which may be lessened by increased breathing and loss of acid through vomiting. Blood phosphorus increases greatly and calcium falls, resulting in

nervous hyperirritability and muscular twitchings. Convulsions may occur when the uremia is associated with hypertension.

Other than the damaged kidneys, there are no constant anatomic changes in uremia. Edema of the brain is common. A mild to severe sterile pericarditis is occasionally present, and degenerative changes have been described in outer portions of myocardium. However, there appear to be no specific myocardial changes in uremia. In some cases of uremia, electrocardiographic changes are indicative of hyperpotassemia. Necrotizing colitis is an occasional occurrence in uremia, and sometimes gastroenteritis also is present. Pulmonary changes with edema may be prominent (see page 670).

In occasional cases of widespread renal damage there is excessive loss of water, sodium, and chloride. This produces an electrolyte disturbance resembling that of Addison's disease (adrenal cortical deficiency—see page 1034) which may be simulated clinically. However, such "salt-losing nephritis" is not benefited by adrenocortical hormone.

Treatment of acute renal insufficiency due to reversible acute renal lesions (e.g., some chemical nephroses) by the "artificial kidney" or by peritoneal lavage has given some promise of success. Extrarenal excretion through the peritoneum may possibly tide over a short period of acute temporary insufficiency.

Extrarenal azotemia is a pronounced retention of nitrogenous metabolites not caused by disease of the kidneys. Azotemia may result from low blood pressure and from the dehydration of decreased fluid intake, excessive diarrhea, or obstruction of the small bowel. In intestinal obstruction, in addition to loss of fluid in the vomitus, there is excessive loss of chloride and hypochloremia. Azotemia also may occur post-operatively and in the terminal stage of a large variety of conditions. Massive gastrointestinal hemorrhage and sometimes subarachnoid hemorrhage may be associated with azotemia. There appear to be several mechanisms which bring about extrarenal azotemia, and it is often difficult to make a sharp distinction from conditions in which there is tubular damage and associated urinary suppression.

Renal Edema.—Edema in chronic nephritis is influenced by two factors: (1) loss of plasma albumin and (2) salt retention. The albuminuria is due to increased permeability of the glomerular tufts, and the protein loss decreases the osmotic pressure exerted by plasma colloids to hold fluid within the vessels. The sodium chloride retention is due to lessened ability of the damaged kidney to excrete it. Lowering of plasma albumin is the more important factor. Edema tends to appear when plasma protein is lowered below 5 Gm. per 100 c.c. (normal is about 6 to 8 Gm. per 100 c.c.). Loss of albumin is particularly important, because it exerts four

times the osmotic force of globulin. In the so-called "nephrotic" types of renal disease a massive albuminuria and severe edema go hand in hand (see page 575).

The distribution of edema in nephritis is often independent of gravity and may appear first on the face rather than in dependent parts. The edema fluid has a very low protein content and low specific gravity.

FOCAL GLOMERULONEPHRITIS

Focal glomerular lesions are commonly found in subacute bacterial endocarditis, in addition to larger areas of infarction which involve the kidney as well as other organs. The term focal embolic glomerulonephritis has been used for such cases, with the implication that the glomerular lesions are due to showers of tiny emboli from the infected cardiac

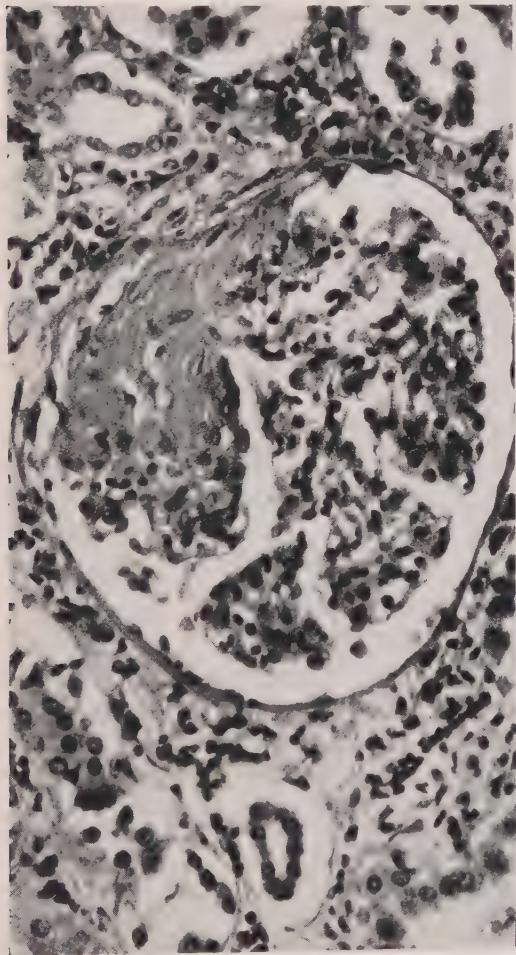


Fig. 440.—Focal glomerulonephritis. (AFIP No. 80093.)

valves which lodge in and damage glomerular capillaries. However, there is much evidence that this embolic theory of pathogenesis is not correct. Only a small proportion of glomeruli are affected, and renal function is not seriously disturbed in most cases. The presence of this renal complication of endocarditis may be manifested clinically by hematuria.

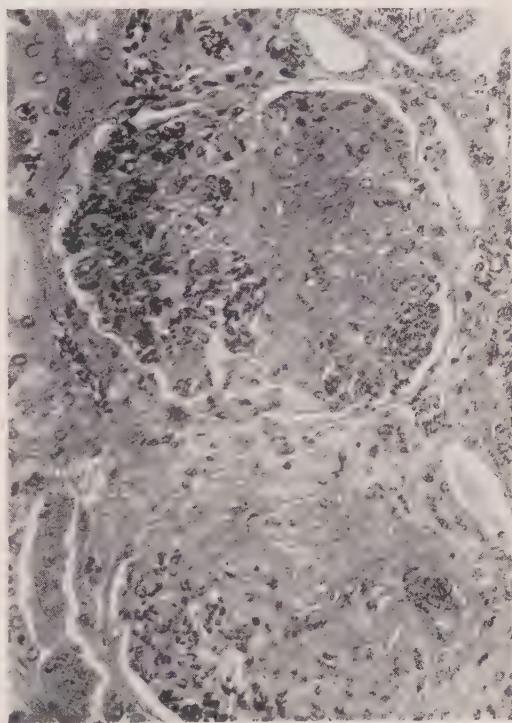


Fig. 441.—Focal glomerulonephritis. From a case of subacute bacterial endocarditis.

The kidneys may be slightly enlarged, have nonadherent capsules and smooth surfaces. The outer and cut surfaces of the cortex tend to be pale, and show small scattered reddish dots or tiny petechial areas, which have been described as giving the kidney a "flea-bitten" appearance. Microscopically, occasional glomeruli show a portion of the tuft involved by hyaline necrosis or so-called "hyaline thrombi." These seem to be small areas of hyaline capillary thrombosis as a result of injury of the glomerular capillary, rather than tiny areas of infarction. Sometimes red blood cells in the adjacent capsular space or some

leukocytic infiltration may be associated with the focal hyaline thrombi. Bell has described also a fibrous type of local glomerular lesion, which begins as a localized proliferative process, rather than being a late stage of the hyaline necrotic change.

A diffuse proliferative glomerulonephritis also occurs in some cases of endocarditis, and may give rise to insufficiency of renal function.

A different variety of focal glomerulonephritis is sometimes found in bacterial infections with bacteremia other than cases of endocarditis. Focal proliferative and exudative glomerular lesions in such cases appear to be due to injury of glomerular capillary walls by bacteria, which often are demonstrable in the lesions.

HEMORRHAGIC GLOMERULONEPHRITIS

Benign and severe forms of hemorrhagic nephritis have been described. In benign hemorrhagic nephritis, which usually occurs in children, a sore throat or upper respiratory infection is followed by hematuria without other clinical evidences of renal involvement. The hematuria soon disappears following subsidence of the infection. The underlying renal lesions are not known.

Severe hemorrhagic nephritis has been described in certain septicemias with hematuria and uremia. There is a relatively massive hemorrhage from ruptured glomerular capillaries, and red blood cells are packed in capsular spaces and tubular lumina. There is an absence of the proliferative and obstructive lesions of glomerular capillaries which characterize true diffuse glomerulonephritis.

Renal Disease of Vascular Origin

The very abundant blood supply of the kidneys is designed not only for nourishment of the tissues but is concerned with the function of the kidneys in regulating the composition of the blood. A free flow of blood through the glomerular capillaries with a relatively high hydrostatic pressure is essential for the function of glomerular filtration. The amount of glomerular filtrate depends upon the quantity and the hydrostatic pressure of the blood passing through the glomeruli as well as upon their total filtration surface. Any lesion which interferes with a sufficient quantity of blood under adequate hydrostatic pressure passing through glomerular capillaries will decrease competent renal function.

One of the peculiarities of the vascular system in the kidneys is that there are two systems of capillaries, the glomerular and the peritubular, which carry the same blood but at widely different hydrostatic pressures. The glomerular capillaries join to form efferent arteries through which blood leaves the glomeruli. The short efferent arteries quickly break up into a meshwork of capillaries which surround and supply the corresponding tubules. Thus the tubules are largely dependent for their blood supply on the free flow of blood through the glomerular capillaries, and when this is reduced or obstructed, the tubules tend to atrophy. The functional activity of the kidneys is thus peculiarly dependent on maintenance of adequate and efficient blood supply. An important group of renal disturbances arises from vascular disease or lesions which interfere with the free flow of blood through the kidneys. The most important of this group of renal diseases result from sclerosis of renal arteries or arterioles, the resulting renal changes commonly being referred to as nephrosclerosis.

Sclerosis of renal arteries and intrarenal vessels is extremely important also because of the association of these changes with high blood pressure. Ischemic renal tissue releases into the blood stream a pressor substance which produces hypertension by constriction of peripheral vessels. Hypertension may be the result of atherosclerosis of a renal artery in those rare instances in which the lumen is constricted sufficiently to cause renal ischemia. In the usual case of hypertension, however, renal ischemia is associated with sclerosis of the smallest arteries or arterioles of the kidney. Sclerosis of the larger arteries within the renal substance is usually irregular and not generalized in its distribution. Hence it rarely causes ischemia of sufficient renal tissue to produce hypertension, nor is there enough destruction to cause renal failure. It produces a few large, gross scars, similar to healed areas of infarction. Because it is a common finding in the elderly, such a kidney is called a "senile arteriosclerotic kidney."

The Senile Arteriosclerotic Kidney (Atherosclerotic Nephrosclerosis).—The atherosclerotic involvement of larger and

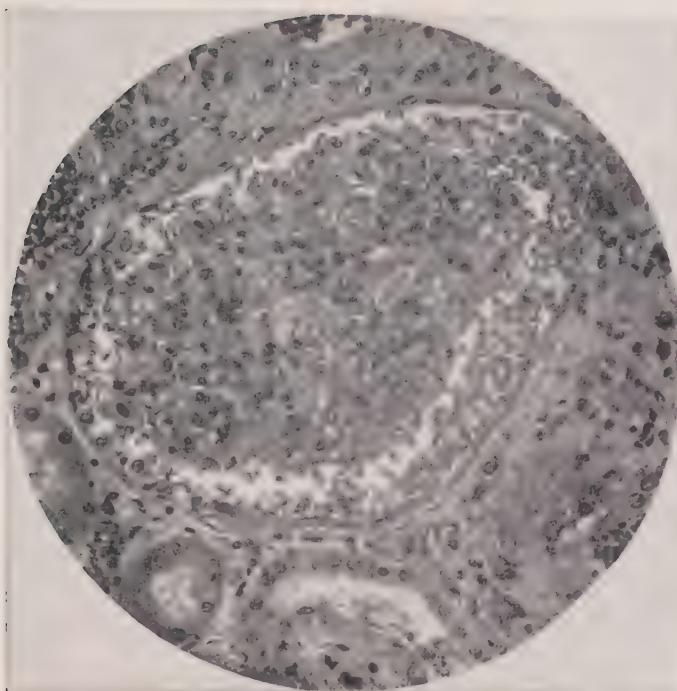


Fig. 442.—Acute glomerulonephritis; hemorrhagic type. The glomerular space is filled with erythrocytes. (Courtesy Dr. F. D. Murphy.)

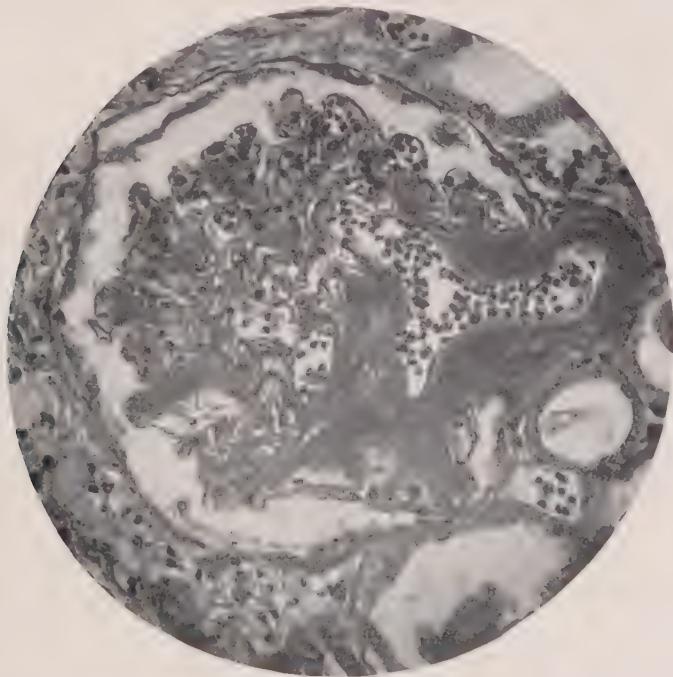


Fig. 443.—Hypertensive nephrosclerosis. Note the hyalinization of the afferent arteriole of the glomerulus, with extension of the process into the glomerular tuft. (Courtesy Dr. F. D. Murphy.)

medium-sized intrarenal arteries is a patchy change which results in irregular depressed areas on the kidney surface. The kidney is not much decreased in size unless there is some other pathologic change. Microscopically, fibrous replacement of glomeruli and tubules is present in the scarred subcapsular portions of the cortex. There is some cellular infiltration by lymphocytes and plasma cells. These changes in the kidney rarely are associated with any marked hypertension or renal functional failure.

In some cases an atherosclerotic lesion of a renal artery, usually at or near its aortic opening, sufficiently narrows the lumen to produce renal ischemia and hypertension.

Hypertension.—Cases of high blood pressure commonly are divided into "secondary" and "essential" types. The less common secondary type is the result of glomerulonephritis, or of an adrenal or pituitary tumor. The common "essential" hypertension was so called because there seemed to be no primary lesion. It has been recognized that renal arteriolar sclerosis is an almost constant postmortem finding in essential hypertension. The arteriolar sclerosis is often a generalized change, particularly common in spleen, pancreas, adrenals, and brain, but it is only in the kidneys that arteriolar sclerosis and hypertension seem to be closely associated. However, biopsy of the kidneys in hypertensive patients has shown that as many as 28 per cent may have little or no vascular change.

The importance of renal vascular changes in hypertension has been shown by Goldblatt, who produced renal ischemia by means of a clamp on the renal artery. It was demonstrated that the ischemic renal tissue released a pressor substance into the circulation, which by constrictive action on peripheral vessels produced hypertension.

A pressor substance ("renin") has been extracted from renal tissue. It is a thermolabile, enzymelike substance which requires for its activity a protein-like substrate present in normal serum ("renin-activator"). The product of their interaction ("angiotonin") produces a prolonged rise in blood pressure. As a possible origin of pressor substance, the "juxtaglomerular" or "preglomerular cellular apparatus" has been suggested. This is an aggregation of granular cells in the afferent arterioles of the glomeruli. While these cells have been noted to increase

in number and prominence in experimental hypertension in animals, there appears to be no parallelism between the degree of development of these cells and hypertension in man.

Essential hypertension has been divided into "benign" and "malignant" clinical types. They appear to be fundamentally the same in nature. The "malignant" form occurs particularly in young adults. It is more rapidly progressive and has severer lesions, but it is of the same general type, and death usually results from renal failure. Pathologically, the malignant form is characterized by necrosis in the walls of small arteries and arterioles, and small hemorrhages from the severely damaged vessels. These necrotizing vascular changes can be reproduced experimentally by renal ischemia sufficient to cause renal failure.

Common causes of death in hypertension are cerebral hemorrhage, renal failure (uremia), congestive heart failure, and coronary occlusion. Cardiac hypertrophy (left ventricle) is a constant finding in cases of hypertension. Retinal changes are also a constant part of hypertensive disease and consist of sclerosis of small retinal vessels, small hemorrhages, and edema. In the malignant phase retinal changes are severe and may result in blindness.

The basic causation of hypertension is still unknown. Hereditary and racial tendencies are important. The American Negro has hypertension more frequently and in severer form than white people in the same climate. Body build and, to a lesser degree, obesity seem to have some association with hypertension.

The Kidney of Hypertension (Arteriolar Nephrosclerosis).—In hypertension the most constant finding in the kidney is a sclerosis of arterioles. Often the smallest preglomerular vessels show the change most severely in the portion just proximal to the tuft. In many cases the kidneys are of normal size and have smooth surfaces. With more severe or prolonged hypertension any degree of atrophy may be found. The capsules are adherent, and the outer surfaces of the kidneys present a finely granular and scarred appearance. Tiny retention cysts are often present in the cortex. For such changes of vascular origin, the term "primarily contracted kidney" is used to distinguish it from the "secondarily con-

tracted kidney" of glomerulonephritis. In practice it is often impossible to distinguish grossly the contracted kidney of hypertensive nephrosclerosis from that of chronic glomerulonephritis.

In malignant hypertension the kidneys often show but little atrophy, due to rapid progress of the disease. Small hemorrhages on the outer surface of the kidney may cause it to resemble the "flea-bitten" kidney of embolic glomerulonephritis.

Microscopically, the essential lesion is a sclerosis of small arteries and arterioles. The effects of the vascular changes are reflected in the glomeruli, which early show a thickening of the capillary basement membranes, and later varying degrees of hyalinization and atrophy. Glomerular capsules as well as tufts become thickened and hyalinized. The atrophy of glomeruli and associated tubules produces the renal shrinkage.

In malignant hypertension the important change is an acute necrotizing arteriolitis and arteritis. The pathologic findings differ somewhat, depending on whether the hypertension was malignant from the beginning, or a benign hypertension with a superimposed malignant terminal phase. In the latter case, varying chronic changes with hyalinization and atrophy of glomeruli are present, but in addition to the usual arteriolar sclerosis, one sees a hyaline necrosis of vessel walls, some inflammatory cellular infiltration and often hemorrhage about severely injured vessels. The hyaline necrotic changes may extend to involve glomerular capillaries as well as arterioles and small arteries.

In end stages with marked renal contraction, it is often difficult to distinguish chronic glomerulonephritis and arteriolar nephrosclerosis, even by microscopic examination. Remaining traces of a proliferative inflammatory process, e.g., glomerular crescents, must be searched for as a distinguishing feature.

Diabetic Glomerulosclerosis.—In 1936 Kimmelstiel and Wilson described a peculiar nodular glomerular lesion in cases of diabetes mellitus. It is characterized by rounded, focal, nodular hyaline areas occupying central parts of the glomerular tufts. While originally considered to be an overgrowth and hyalinization of inter-

capillary connective tissue, later studies (Allen, Bell) have indicated that the nodular lesions are derived from capillary walls, and hence are not strictly "intercapillary."

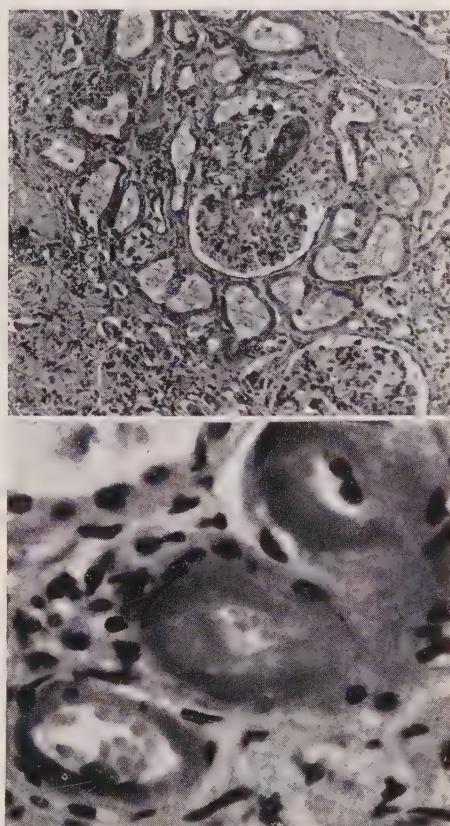


Fig. 444.—Arteriolar nephrosclerosis. Note the severe involvement of the entering arteriole.

The nodular glomerulosclerosis has been found to occur in about one-third of diabetics over the age of 40, but is unusual in individuals under 30 years of age. Its frequency is somewhat greater in females than in males. The lesion appears to be practically pathognomonic of diabetes mellitus, and is a helpful criterion in histologic diagnosis of that disease. The glomerular lesions appear to bear no relationship to the severity or duration of diabetes. No constant clinical syndrome is associated with the lesions, but in some cases there is a marked albuminuria, hypoproteinemia, and edema. Hypertension and retinal arteriosclerosis also may form part of the clinical picture.

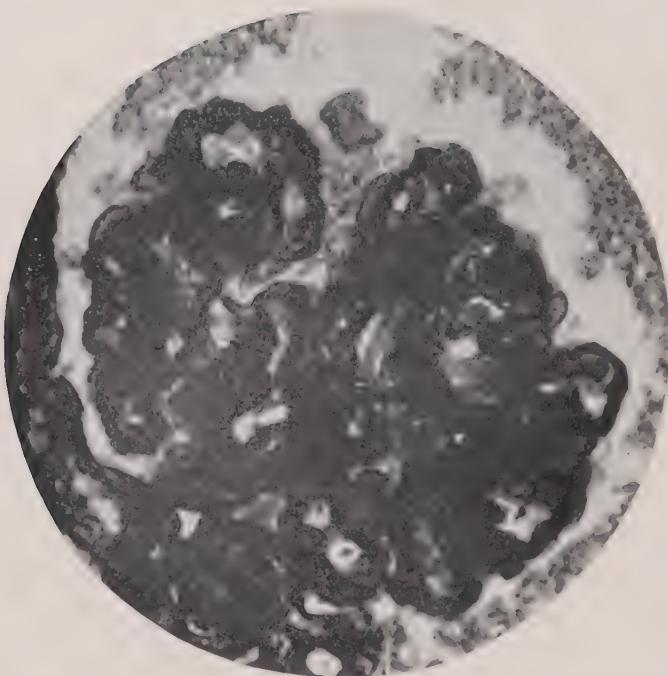


Fig. 445.—Thickening of the basement membranes and capillary walls in a glomerulus. From a case of malignant hypertension. (Courtesy Dr. F. D. Murphy.)



Fig. 446.—Kidney of malignant hypertension, showing focal hemorrhages from arteriolonecrosis.

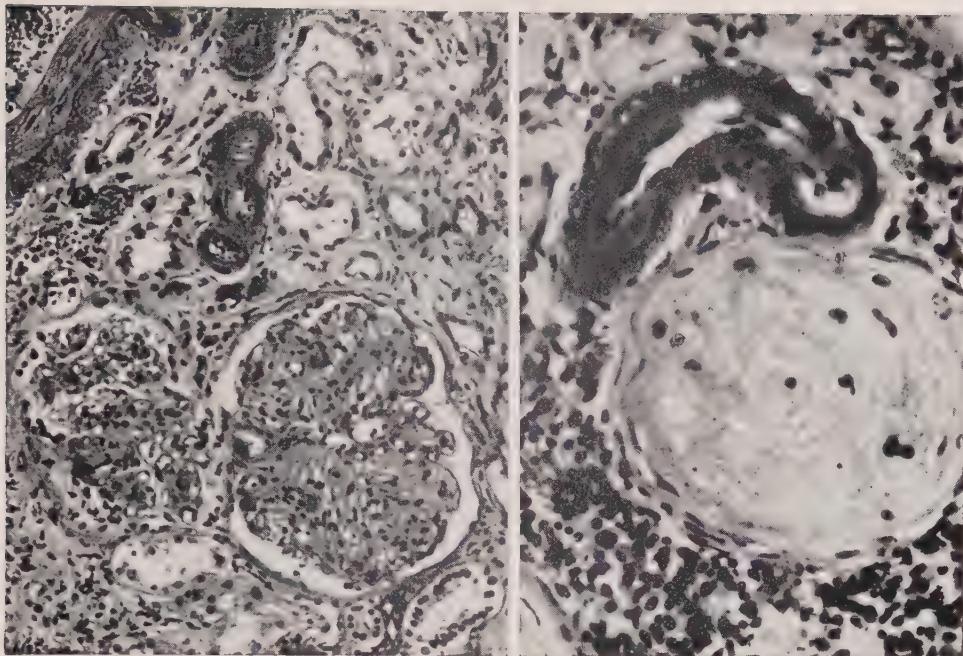


Fig. 447.—Arteriolar nephrosclerosis. Severe hyalinization of blood vessels. From a case of malignant hypertension.

The diabetic glomerulosclerosis is often found associated with considerable renal arteriolosclerosis.

Bell has described also a diffuse form of glomerulosclerosis in diabetics, which is more frequent than the nodular lesions and may be present alone or in association with the nodular lesions.

Other renal lesions in diabetes mellitus include pyelonephritis and papillary necrosis (see page 582) and the presence of large amounts of glycogen in the epithelial cells of the loops of Henle, and sometimes of the convoluted tubules. Such glycogen accumulation, which gives the cytoplasm of the tubular cells a remarkably clear, watery, or vacuolated appearance occurs only in cases uncontrolled by insulin.

Infarction of the Kidneys.—Infarcts occur quite commonly in the kidney in individuals with bacterial endocarditis, auricular fibrillation with intra-auricular thrombi, and coronary occlusions with myocardial infarction. Associated clinical effects may be severe pain in the back, tenderness in the costovertebral angle, nausea and vomiting, and hematuria. Rare cases of extensive renal infarction have been associated with oliguria or anuria and uremia.

Renal Vein Thrombosis.—Renal vein thrombosis is an uncommon condition which may give

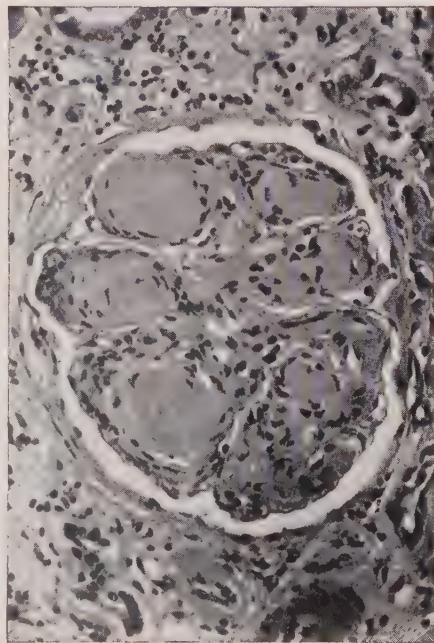


Fig. 448.—Diabetic capillary glomerulosclerosis. (Courtesy Dr. A. C. Allen and the Armed Forces Institute of Pathology.)

rise to hemorrhagic infarction of the kidney, or if the main renal vein is occluded there may be massive renal necrosis. In adults the renal vein thrombosis is usually a secondary extension

from thrombophlebitis of peripheral veins. In childhood a primary renal vein thrombosis may be associated with ileocolitis.

Bilateral Cortical Necrosis of the Kidneys.—There is an unusual condition characterized by

variety of apparently unrelated conditions. Apart from pregnancy it has occurred most often during the course of various infections, such as scarlet fever, diphtheria, pneumonia, tonsillitis, dysentery, etc. A similar renal lesion

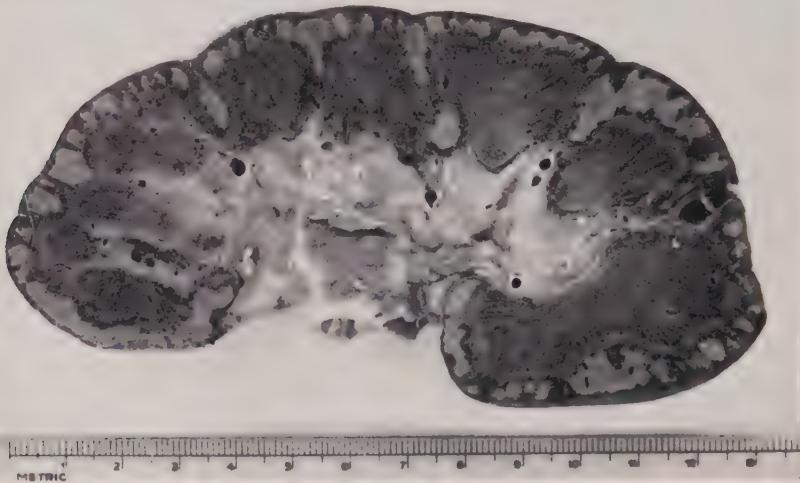


Fig. 449.—Cortical necrosis of kidney. A reddened congestive zone outlines the opaque necrotic cortical tissue.

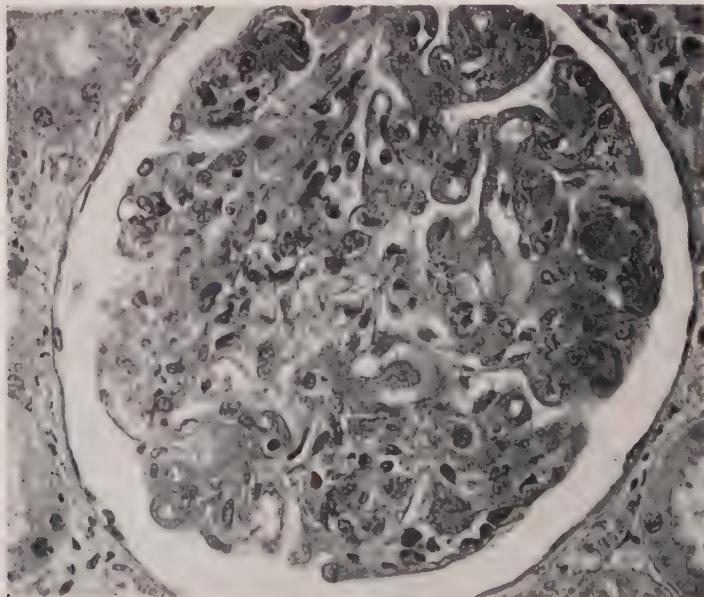


Fig. 450.—Kidney in disseminated lupus erythematosus, showing "wire loop" lesions and fibrinoid necrosis of a glomerulus.

extensive, rather complete, and uniform necrosis of the cortex of both kidneys. While a number of cases have been associated with a toxemia of late pregnancy, other cases have occurred in the absence of pregnancy, at various ages in both sexes and associated with a

has resulted from poisoning by dioxane or diethylene glycol, and in experimental animals has resulted from choline deficiency.

Oliguria or anuria occurs with the onset of the disease, sometimes accompanied by pain or tenderness in the epigastrium or loins. Death

usually occurs in four to twelve days. The kidneys are found to be slightly enlarged and swollen, softer than normal, and with capsules which strip away easily leaving smooth surfaces. The outer surface shows some irregular patchy mottling of reddish-yellow color. On the cut surface, which bulges slightly, the cortex is largely composed of yellowish opaque areas of necrosis, which are irregular in outline, and may extend to include the columns of Bertin. A thin subscapular zone of the cortex and an inner zone of cortex and adjacent medulla may be congested and reddened, outlining the yellowish necrotic area. Microscopically there is widespread infarctlike or coagulative necrosis of the cortex, the necrotic areas being bordered by a hemorrhagic or hyperemic zone with leukocytic infiltration. The general architecture of the necrotic tissue is usually evident, although individual components are not discernible or show marked alterations. Arterioles, small arteries, and particularly intralobular arteries show thrombotic occlusions of their lumina, and sometimes necrosis of their walls.

It is generally agreed that the necrosis of the renal cortices is ischemic in origin. It appears to be due to widespread organic or functional occlusion of the intralobular arteries and their branches, the terminal arteries and arterioles of the renal cortices. The actual mechanism of the vascular obstruction, whether by intense vasoconstriction, vasoparalysis, thrombosis, or necrosis of arterial walls, may vary in different cases. The work of Trueta suggests that there may be a vascular mechanism by which most of the cortex is by-passed, the blood being shunted through the medulla.

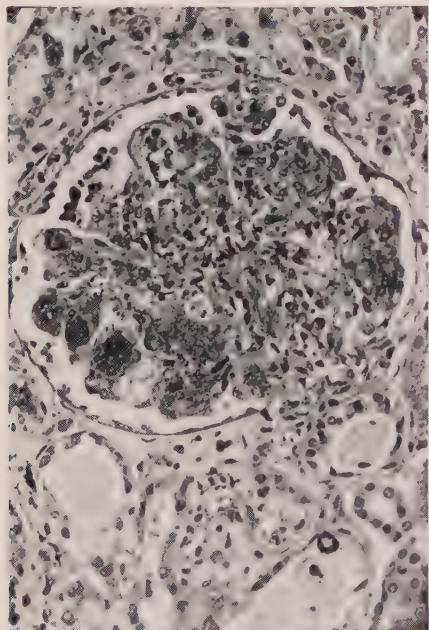


Fig. 451.—Glomerular lesion of the kidney showing endothelial proliferation and hyaline thrombi in a case of disseminated lupus erythematosus. (Courtesy Dr. A. C. Allen and The Armed Forces Institute of Pathology.)

Renal Lesions in Disseminated Lupus Erythematosus.—Renal lesions are common in disseminated lupus erythematosus, but are not invariable, and no single type of change is constant or pathognomonic. The kidneys are of normal size or slightly enlarged. Proliferation of endothelial cells of the glomerular capillaries appears to be most common. A patchy

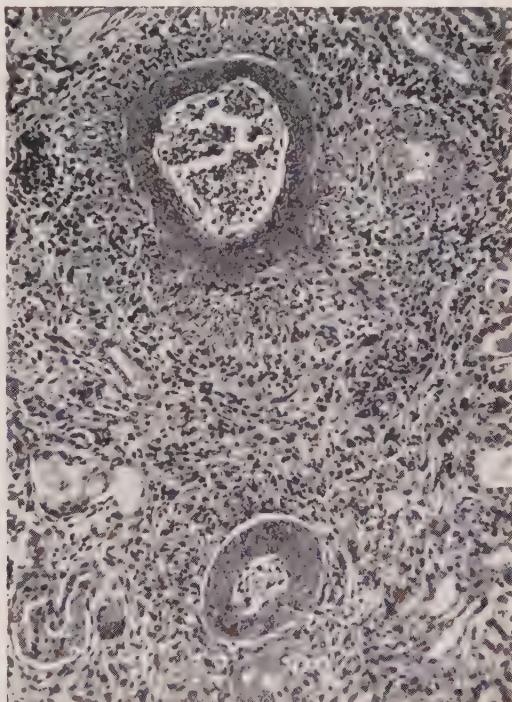


Fig. 452.—Kidney, periarteritis nodosa.

hyaline thickening of the basement membranes of the glomerular capillaries, giving a "wire-loop" appearance, has been described as most characteristic, but is often absent. Intracapillary hyaline "thrombi" are seen in the glomeruli in some cases. The urinary sediment in lupus erythematosus shows unusual features which may be helpful in diagnosis. Krupp has described the unique association of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein.

Periarteritis Nodosa of the Kidneys.—The kidneys are among the organs most frequently affected by periarteritis nodosa, an acute inflammation and necrosis of the walls of small arteries (see page 529). Hypertension and renal insufficiency may accompany the renal involvement in periarteritis nodosa. The renal lesions, both grossly and microscopically, may closely resemble those seen in certain cases of malignant hypertension. In some cases of periarteritis nodosa one may find numerous small areas of infarction or necrosis of the renal tissue, associated with acute necrosis of the walls of small arteries. The involved vessels are thrombosed and show extensive leukocytic infiltration in and around their walls. The leuko-

cytic reaction usually tends to be more marked than in the case of the arteriolar necrosis in the kidney of malignant hypertension. Vascular lesions in the kidney similar to those of periarteritis nodosa may occur from sulfonamide hypersensitivity.

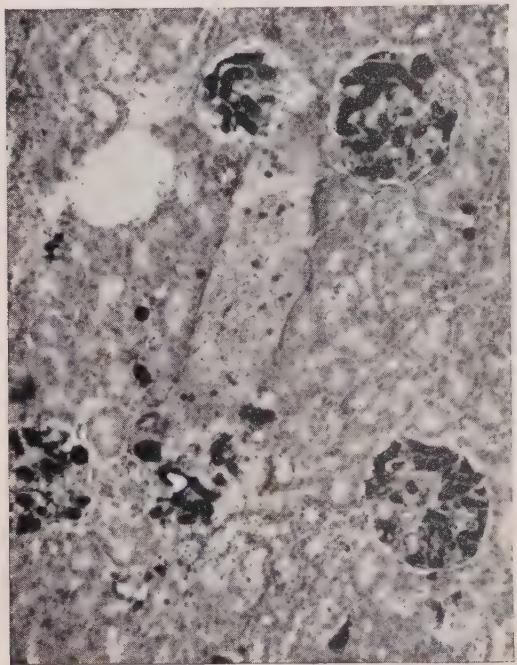


Fig. 453.—Fat embolism of the kidney. The fatty material is stained black. (Courtesy Dr. A. C. Allen and The Armed Forces Institute of Pathology.)

Orthostatic Albuminuria.—Orthostatic or benign albuminuria is a clinical condition in which there is urinary excretion of albumin when the individual is erect, but not when lying down. It appears to be due to circulatory changes in the kidneys when the individual is in a lordotic position. Abnormalities described in such cases include (1) compression of the left renal vein between the superior mesenteric artery and the aorta, (2) mobile kidneys, and (3) reduplicate ureters and pelves.

Nephrosis

The term "nephrosis" was originally applied to degenerative or retrogressive renal lesions, as distinct from inflammation (nephritis) or vascular disease (nephrosclerosis). As the degenerative changes are seen mainly in the tubules, and particularly in the sensitive convoluted tubules of the cortex, some have preferred to use the term "tubular nephritis" for this type of lesion. Neither term is satisfactory and without serious

disadvantages, but "nephrosis" has become thoroughly ingrained by common usage. Unfortunately, a clinical usage of the term "nephrosis" has developed, referring to any renal disease clinically characterized by marked albuminuria, massive edema, hypercholesterolemia, and absence of hematuria, but without any marked hypertension or nitrogen retention, even though underlying this clinical syndrome may be more than one type of pathologic change in the kidneys. This clinical syndrome is most often a stage in the course of glomerulonephritis, and its manifestations are the reflection of a glomerular injury with hyperpermeability of the glomerular filter, rather than the effect of a tubular lesion. Although recognizing this common clinical meaning of "nephrosis," the term will be used herein to refer to the types of renal injury which appear to be primarily degenerative in their nature.

Most renal diseases, including glomerulonephritis, have associated degenerative changes, particularly in the convoluted tubules. However, nephroses in which degeneration appears to be the primary and predominant process can be divided into three groups: (1) chemical nephroses, renal injuries resulting from exogenous poisons; (2) nephroses of toxic or metabolic origin, due to toxins resulting from infections or of endogenous origin from disturbed metabolism; and (3) lipoid nephrosis, a rare but apparently distinct disease entity, characterized by hyperpermeability of glomerular capillaries, disturbance of protein levels, and accumulation of lipoid in renal tubules.

Chemical Nephrosis.—A variety of poisons, including mercury bichloride, uranium nitrate, potassium bichromate, and carbon tetrachloride, may cause degeneration and necrosis of tubular epithelium.

Renal lesions due to mercury bichloride are most frequently encountered. This poison causes a pure tubular injury of severe grade; and after ingestion of fatal doses, those patients who do not die of shock within the first day develop oliguria, which usually progresses to anuria and death in uremia. Death occurs most frequently between the fifth and the tenth days, at which stage the kidney is swollen and grayish-white in color. The

epithelium of the proximal convoluted tubules is necrotic, broken up, and irregularly desquamated. The interstitial tissue is edematous and often infiltrated by leukocytes. After seven to ten days the kidney appears more red and congested, and calcium is often deposited in the degenerated and necrotic tubular epithe-

lium. Evidences of epithelial regeneration may be evident at this time. Some of the convoluted tubules may be lined by newly formed, flat, darkly staining cells, and mitotic nuclei may be found. In non-fatal cases such newly formed epithelium may be more resistant to the effects of the poison. In experimental animals

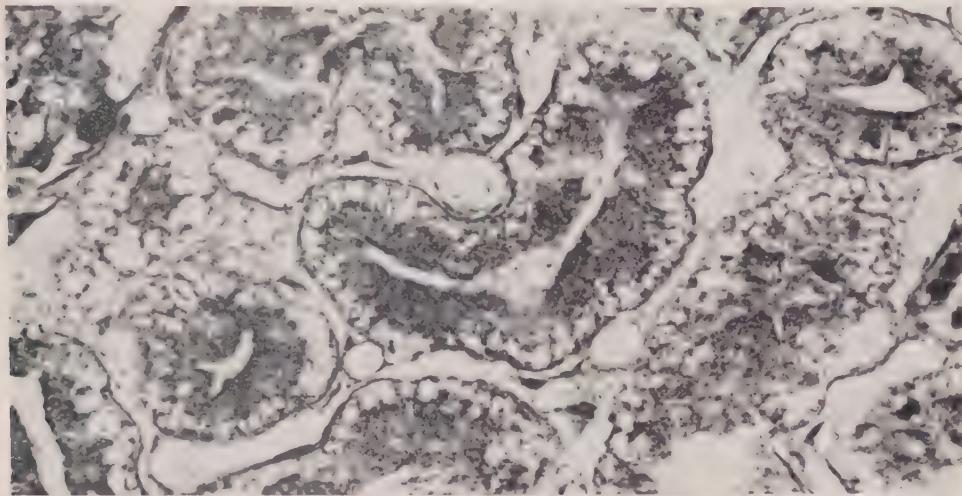


Fig. 454.—Carbon tetrachloride nephrosis. Note the fatty vacuoles, particularly in the basal parts of the tubular epithelium.

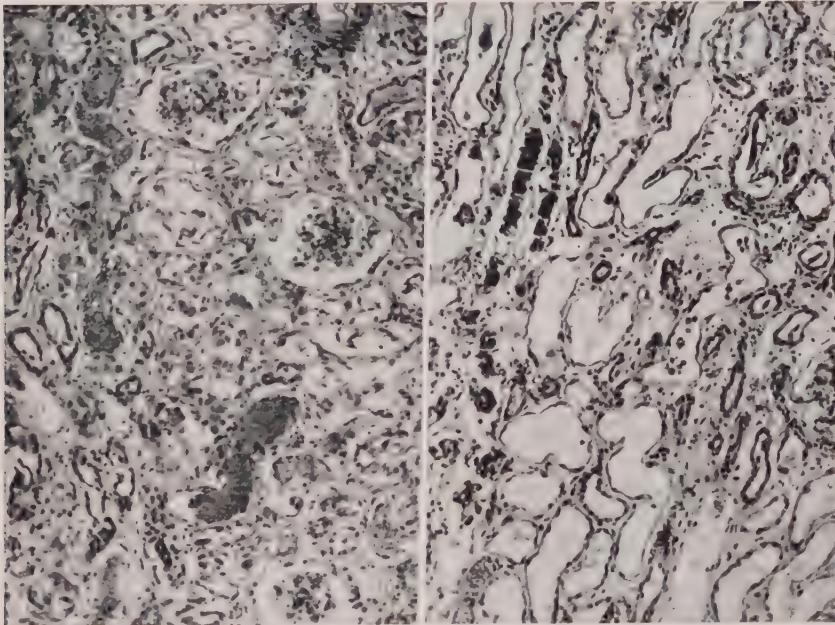


Fig. 455.—Kidney, mercury bichloride poisoning. Left: Kidney seven days after ingestion of mercury. Note desquamation and destruction of tubular epithelium. Right: Kidney on eleventh day. Note loss of tubular epithelium, flattened tubular lining, and dark calcium masses in tubular lumina.

testosterone gives some protection against the damaging effect of mercury bichloride.

The selective action of mercury bichloride on the proximal convoluted tubules appears to be due to concentration of the poison which occurs in this portion of the nephron. The oliguria and anuria which occur may be due to failure of formation of a glomerular filtrate, but have been attributed by some to excessive reabsorption of the glomerular filtrate into the peritubular capillaries in the absence of the selective and restraining influence of the tubular epithelial lining.

fuse, form larger bodies, and probably are eliminated in the lumens of the tubules. Functional change from sucrose nephrosis in an otherwise normal kidney apparently is not severe, and the lesion is but temporary. Gelatin administered intravenously may produce a tubular change similar to that resulting from sucrose. It is possible that much of the swelling of the tubular cells seen microscopically is due to absorption of fluid during preparation of the tissue.

Toxic and Metabolic Nephrosis.—

Nephrosis of toxic or metabolic origin is

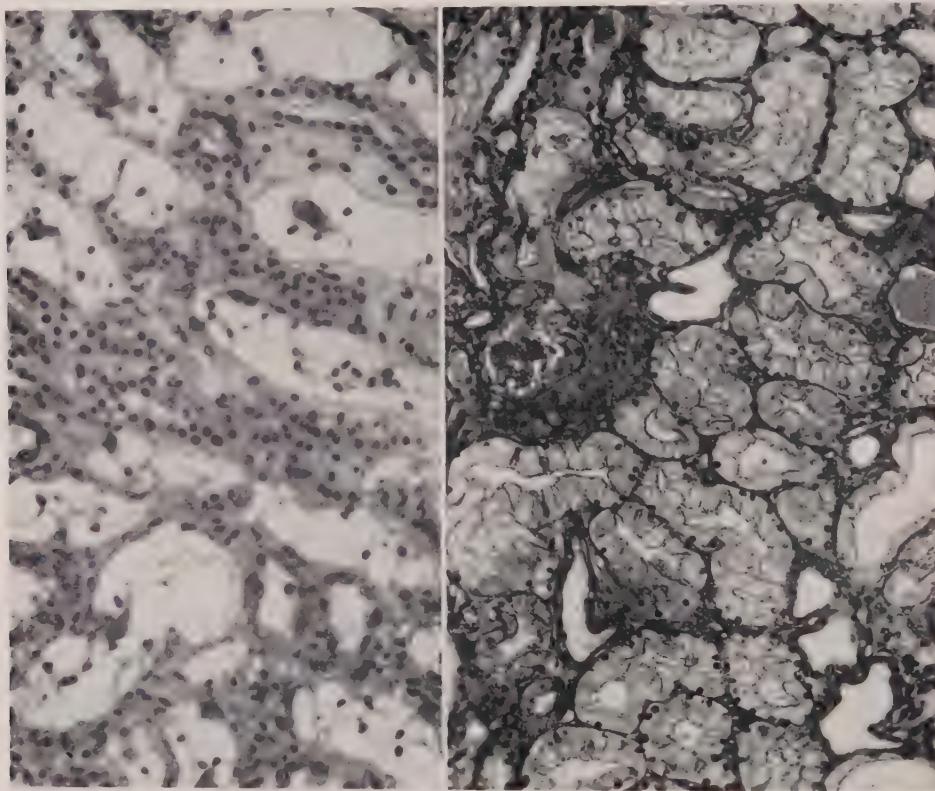


Fig. 456.—Hydropic degeneration of the kidney. Left: Hydropic degeneration following poisoning by diethylene glycol. Right: Hydropic degeneration following injection of hypertonic solutions of sucrose.

Uranium nitrate injures the kidney in a fashion similar to mercury bichloride, and has frequently been used experimentally to produce renal injury. Carbon tetrachloride has also been shown to produce tubular degeneration.

Dioxane and diethylene glycol produce a severe hydropic degeneration of the tubules, and in fatal doses have produced large areas of hemorrhagic necrosis in the renal cortex. Sucrose, when given intravenously in hypertonic solution, will produce the appearance of severe hydropic degeneration of the renal tubular epithelium in microscopic sections. The sucrose appears to be stored in the mitochondria, which

the commonest form of tubular change. Most acute infectious and toxic conditions cause tubular lesions, which may be cloudy swelling, fatty degeneration, hyaline droplet degeneration, or even necrosis of epithelial cells. Hyaline and lipid droplets indicate absorption from the tubular lumina and storage in the lining epithelial cells of protein and lipid material which has passed through damaged, abnormally permeable, glomeruli.

Cholemic nephrosis is the renal injury accompanying severe jaundice. In addition to numerous yellowish pigment casts filling tubular lumina, especially the collecting tubules of the medulla, degenerative changes of mild degree are often evident in the cells of the convoluted tubules. It is uncertain whether the injury is due to bile pigments, bile salts, or to associated hepatic damage. Injuries and operative pro-

hemoglobinemia, and discussed on pages 131 and 588.

Intestinal obstruction, particularly when high in the intestinal tract (e.g., pyloric stenosis), may produce tubular degeneration, sometimes with calcification of the degenerated cells.

A distinctive vacuolar lesion of the proximal convoluted tubules (**vacuolar nephropathy**) occurs with some cases of chronic intestinal dis-

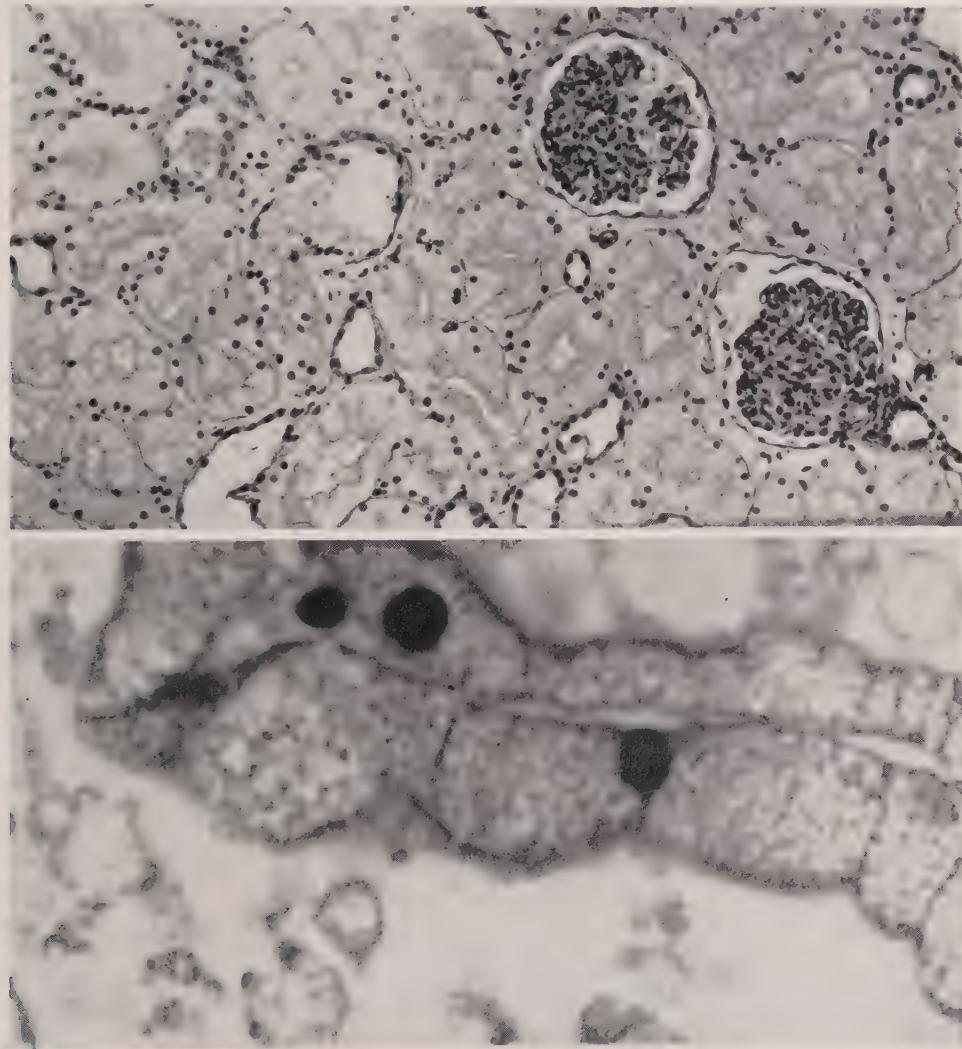


Fig. 457.—Sucrose nephrosis. Severe hydropic degeneration of tubular epithelium following intravenous injection of hypertonic solutions of sucrose.

cedures upon the liver and biliary tract are sometimes complicated by marked renal functional disturbance, for reasons as yet unexplained (hepatorenal syndrome, see page 808).

Severe thermal burns may be complicated by renal injuries in which tubular degeneration plays a part. Similarly, other traumatic and crushing injuries and shock may affect the kidney, the lesions being similar to those of

diseases (e.g., ulcerative colitis, regional enteritis). Large clear vacuoles, which fail to react to stains for fat or glycogen, balloon out the tubular cells. Signs of renal dysfunction are inconstant and fail to correlate with the severity of the vacuolation.

Lipoid Nephrosis.—Lipoid nephrosis is an uncommon disease of children and

young adults in which there is a massive albuminuria, with low plasma protein, reversal of the albumin-globulin ratio in the blood, marked edema, hypercho-

the sense of retention of nitrogenous products and development of uremia is lacking. Hypertension is also absent. However, so-called "mixed forms" occur,

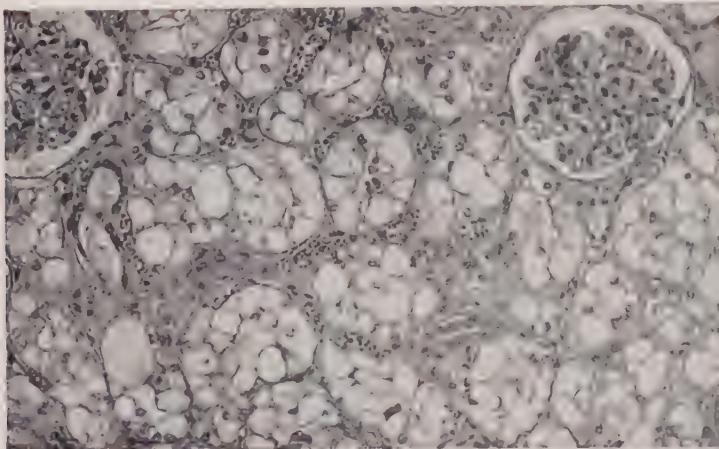


Fig. 458.—Vacuolar nephropathy, from a case of regional enteritis. (Courtesy Dr. J. F. Kuzma. From Anderson, Synopsis of Pathology.)

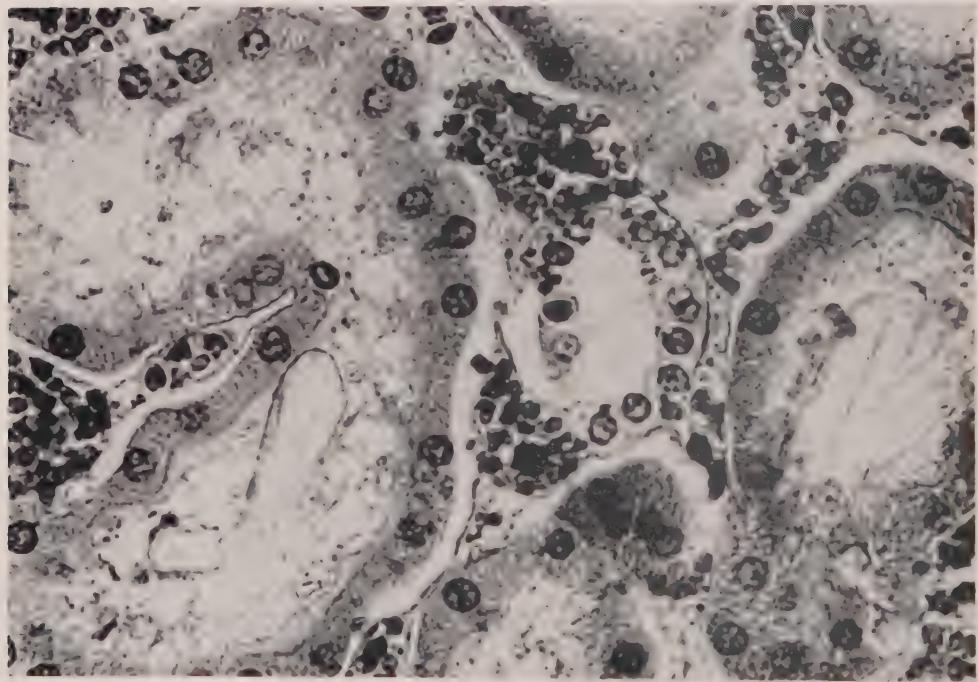


Fig. 459.—Ethylene glycol nephrosis, following ingestion of "anti-freeze" solution. Calcium oxalate crystals can be seen in the tubular lumina. (AFIP No. 88718.)

lesterolemia, increased susceptibility to infection, and low basal metabolism. Doubly refractile lipoid appears in the urinary sediment. Renal insufficiency in

which are examples of glomerulonephritis with marked albuminuria and edema in addition to renal insufficiency and hypertension.

The kidneys are usually slightly enlarged or of normal size. The surfaces are smooth and the capsules are not adherent. The renal tissue is pale or grayish-white in color, but a faint or definite yellowish tinge or streaking may be seen in the cortex. Architectural markings remain distinct, and no changes are evident in the medulla or pelvis.

Microscopically, the only constant change is an accumulation of lipoidal material in the cells of the proximal convoluted tubules. Some of this lipoid is anisotropic fat, and shows double refractivity when examined with polarized light. The degree of fatty change in the tubules varies from slight to marked. Some of the doubly refractile lipoid is found in debris in the tubular lumina, and is excreted in the urine where its presence may be found in urinary sediment. The presence of lipoid in the tubular cells probably does not seriously interfere with their function. Some tubules may be dilated or show other types of degenerative change.

The glomeruli usually show only inconspicuous morphologic changes. The condition has also been termed membranous glomerulonephritis. The hyperpermeability of the glomerular capillaries, which appears to be the fundamental abnormality in this disease, is not reflected by microscopic findings which can be correlated. Bell has emphasized the occurrence of thickening of the basement membranes of the glomerular capillaries, but usually with little or no proliferation of endothelial cells. The capillary lumina are not narrowed or obstructed except in cases in which the basement membrane thickening is severe.

In cases which clinically show a nephrotic syndrome but which are of a "mixed type" rather than a pure lipoid nephrosis, various proliferative glomerular changes characteristic of glomerulonephritis may be found, and in the tubules secondary changes of dilatation, degeneration and atrophy may appear. Thickened basement membranes may be conspicuous. In cases which have exhibited hypertension and evidences of renal insufficiency, the kidneys may be smaller than normal and show gross evidences of scarring.

Lipoid nephrosis usually has a chronic and sometimes a prolonged course, which may be

marked by exacerbations and remissions. A decrease of plasma amino acid marks exacerbations or crises of the disease, especially in children. The duration is most often between six months and five years, but some cases are more acute and some very prolonged. Some cases, perhaps about 25 per cent, appear to recover completely from the disease. Some which appeared clinically to be "pure" lipoid nephrosis later develop hypertension and renal insufficiency, and die with uremia. In such "mixed" cases lesions of glomerulonephritis are found in the kidneys. In the majority of fatal cases, infection supervenes and is the cause of death. This is most often a pneumococcal infection of the peritoneum, but streptococcal infections involving peritoneum, lung, or other tissues may occur.



Fig. 460.—Lipoid nephrosis. Doubly refractile lipoids within the tubular epithelium, as seen with a polarizing microscope. (Courtesy Dr. F. D. Murphy.)

The possibility has been seriously considered that lipoid nephrosis may be primarily a metabolic disturbance of proteins or lipids, with the renal changes but secondary manifestations. However, with present knowledge, it seems best explained as a marked hyperpermeability of the glomerular capillaries to plasma albumin. Loss of large amounts of albumin in the urine accounts for the low level of albumin in the blood, and, as a result of the decreased osmotic force

exerted by blood proteins, for the marked edema. The elevation of blood cholesterol is not so easily explained, but appears to be associated with depletion of plasma proteins. The increased susceptibility to infection may be due to the influence of an associated decrease of gamma globulin.

Interstitial Nephritis

Interstitial nephritis, unlike glomerulonephritis, is essentially an exudative rather than a proliferative inflammation. Marked exudates of inflammatory cells may be present focally or diffusely in interstitial tissue.

Acute Diffuse Interstitial Nephritis.—Acute interstitial nephritis occasionally develops in association with certain acute, infectious diseases, e.g., diphtheria, scarlet fever, Weil's disease, etc. Grossly the kidney is large, pale or mottled red and gray, and soft. The cortex is thickened. The capsule strips easily. Microscopically there is a focal or diffuse interstitial infiltration of leukocytes, mainly plasma cells, lymphocytes, and eosinophiles, but often polymorphonuclear leukocytes as well. It must be distinguished from a leukemic infiltration. The tubules show degeneration but glomerular lesions are usually absent, and the damage is not permanent.

Chronic Interstitial Nephritis.—The rare condition of chronic interstitial nephritis develops as a result of certain types of chronic renal injuries, e.g., in chronic hyperparathyroidism, multiple myeloma, etc. It is characterized by interstitial infiltration by lymphocytes and plasma cells, with degeneration, atrophy, and fibrosis of renal tissue. Distinction from chronic pyelonephritis may be difficult.

Focal Suppurative Interstitial Nephritis (Pyemic Kidney, Abscesses of Kidney).—Lodgment of infected emboli, as part of a generalized pyemia, results in multiple abscesses throughout the kidney substance. The abscesses appear as small, rounded, yellowish opaque areas, surrounded by a reddened hyperemic zone. They may be numerous or a single large abscess may be found. The abscesses apparently begin by lodgment of bacteria in glomeruli, the infection extending by way of tubules, so that it may eventually reach the pelvis, and also directly into

adjacent tissue. Usually multiple focal renal abscesses are found as only part of a generalized staphylococcal pyemia. In some cases colon bacilli also are found.

When a single large abscess, usually multilocular, involves a kidney, it is sometimes referred to as a renal "carbuncle." This may be unilateral, and without pelvic involvement or the appearance of pus in the urine.

Spread of the pyogenic infection to the tissues around the kidney results in peri-nephric abscess. Although usually the result of an area of cortical suppuration breaking through the renal capsule, it also develops independently of renal parenchymal involvement.

Pyelonephritis.—The term "pyelonephritis" is used when both the parenchyma of the kidney and the renal pelvis are involved by interstitial inflammation. "Pyelitis" refers to an inflammation of the renal pelvis alone, and such involvement of the pelvis without any marked spread to the renal parenchyma is unusual. Most cases referred to clinically as pyelitis, commonly in children and pregnant women, are really examples of pyelonephritis.

Pyelonephritis really includes several types and stages of renal interstitial inflammation, with varying pathogenesis and effects. The organisms most commonly involved are colon bacilli and staphylococci. In the majority of cases there is an associated obstruction of the lower urinary tract. Obstructions due to urethral, prostatic, or bladder lesions very commonly are associated with pyelonephritis. The lower end of the ureters are dilated as a result of the lower urinary tract obstruction, which facilitates the ascension of organisms from the infected bladder or prostate. It has also been claimed that infection may reach the renal pelvis from the lower urinary tract by way of the periureteral lymphatics. The "ascending" type of pyelonephritis in which the bladder and renal pelvis are affected first, and spread occurs by ascending to infect renal tissue, probably occurs only when there is obstruction with consequent stagnation of urine. Mild degrees of this type of pyelonephritis are very common in adults of middle age and beyond. It is more frequent in women up to the sixth decade because of

urinary obstructions due to pregnancy and uterine tumors, but after that age the majority of cases are in men, due to the frequency of obstruction from prostatic enlargement.

In many cases of pyelonephritis the infection is hematogenous, organisms reaching the kidney by way of the blood stream from some other primary focus. In these cases, as in the pyemic kidney, the cortex of the kidney is first involved, the infection "descending" by way of the tubules to infect the pelvis. Except for the cases beginning with obstruction, stasis, and infection in the lower urinary tract, a hematogenous origin producing the descending type of pyelonephritis is more common. It has been shown in experimental animals that an obstruction of the urinary tract predisposes the kidney to infection by organisms carried in the blood stream.

changes in glomeruli, tubules, and blood vessels may be very marked.

The kidneys show wedge-shaped areas of inflammation extending through cortex and medulla to pelvis. Microscopically, such areas show interstitial infiltration of inflammatory cells, often with some tubular destruction and abscess formation. In the acute stages, the cells are mainly polymorphonuclear leukocytes, and in chronic phases are lymphocytes and plasma cells. The mucosa of the pelvis is roughened, and masses of lymphocytes are found under the epithelium. Continuation of low-grade interstitial inflammation results in gradual atrophy and destruction of tubules, and hyalinization of glomeruli by a process of periglomerular fibrosis and capsular thickening. Colloid casts are present in enlarged tubules with atrophic epithelium. Eventually there results a kidney

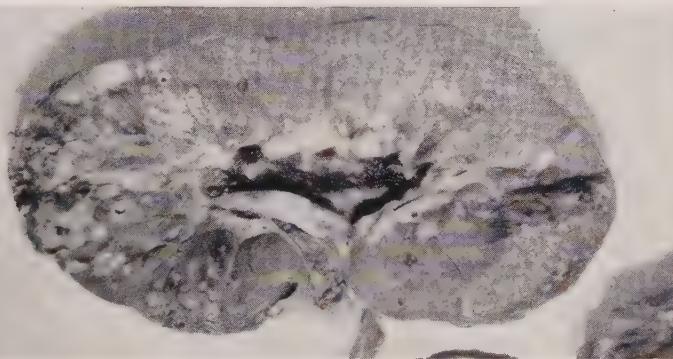


Fig. 461.—Suppurative pyelonephritis. (Courtesy Dr. H. C. Schmeisser.)

The changes in gross and microscopic appearance of the kidneys in pyelonephritis depend upon the stage of the infection; i.e., whether acute, chronic, healed or recurrent, and upon the presence or absence of hydronephrosis. In cases with obstruction of the urinary tract there is usually dilatation of the renal pelvis, which may vary from mild to great degree. The involvement may be unilateral or bilateral. It is characteristic of pyelonephritis that the changes in the kidney are patchy, areas of relatively normal appearance being interspersed with the affected regions. Inflammatory exudate appears predominantly in interstitial tissue, except in some early or acute phases, although secondary

which is coarsely pitted by U-shaped scars, greatly contracted, and of little functional value. Such a pyelonephritic contracture of the kidney is sometimes unilateral and may be difficult to distinguish from unilateral renal hypoplasia. When chronic pyelonephritis is bilateral, its end stages are easily confused clinically and even at autopsy with chronic glomerulonephritis. Vascular changes of medial fibrosis and endarteritis obliterans are frequently associated with chronic and healed stages of pyelonephritis. The exact relationship of chronic pyelonephritis to hypertension is still a matter of some debate. There appears to be no doubt that many cases of chronic pyelonephritis have had an associated hyper-

tension, but some question exists as to whether this is to be ascribed to the pyelonephritic changes or to concomitant vascular or glomerular disease. The problem assumes particular importance in cases of unilateral chronic pyelonephritis,

where surgical removal of the involved kidney might be expected to change the course of the hypertensive disease, particularly if done early before secondary vascular changes elsewhere become advanced. While successful results have

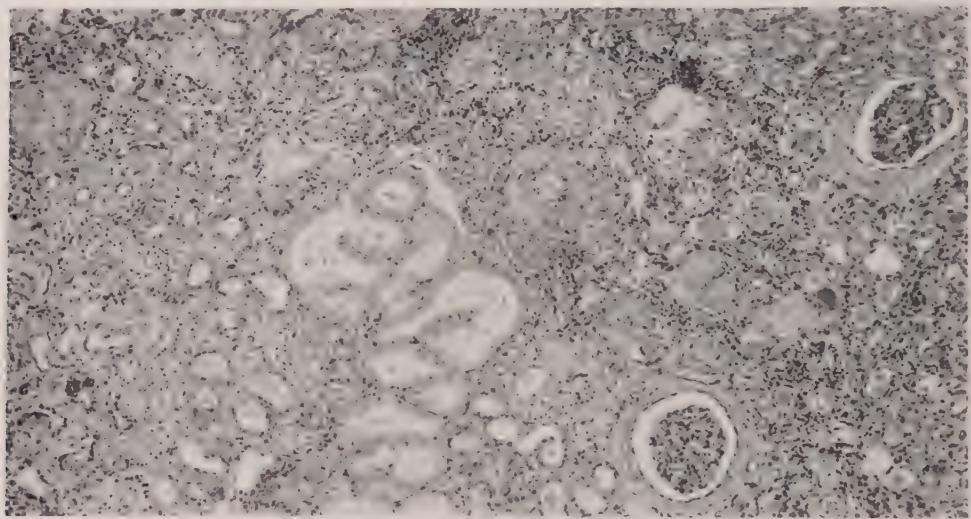


Fig. 462.—Chronic pyelonephritis. Note the capsular thickening of glomeruli, the interstitial fibrosis and cellular infiltrate, the hyaline casts in some tubules, and enlargement of other tubules. (AFIP No. 76640.)

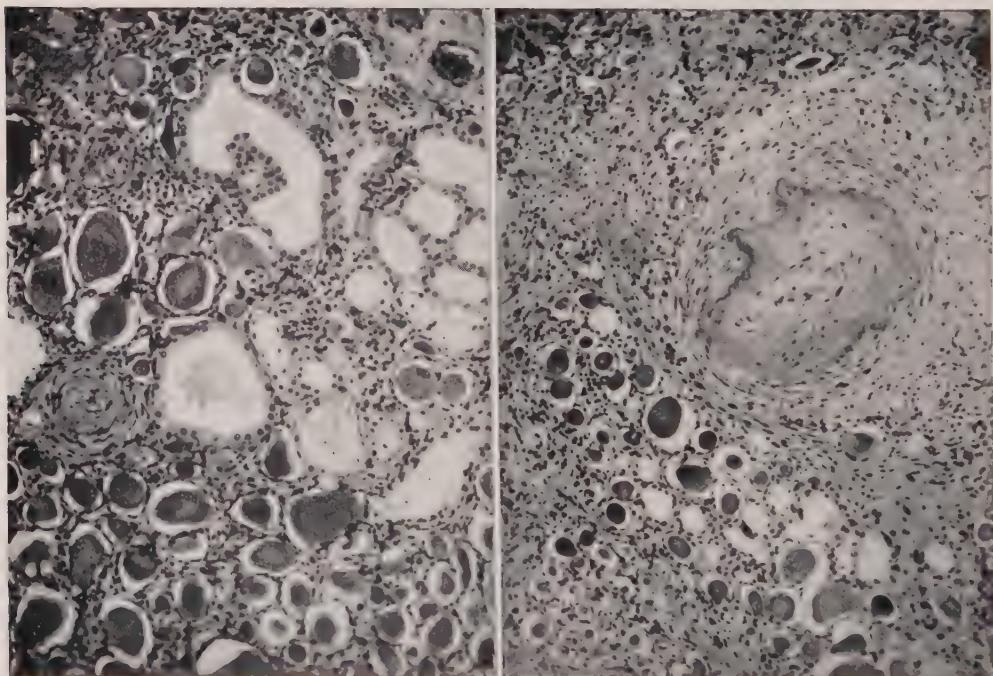


Fig. 463.—Chronic pyelonephritis. Note the dilated tubules filled with hyaline or "colloid" casts and the thickened blood vessels.



Fig. 464.—Papillary necrosis of the kidney. From a case of diabetes mellitus with ureteral stenosis and mild hydronephrosis.

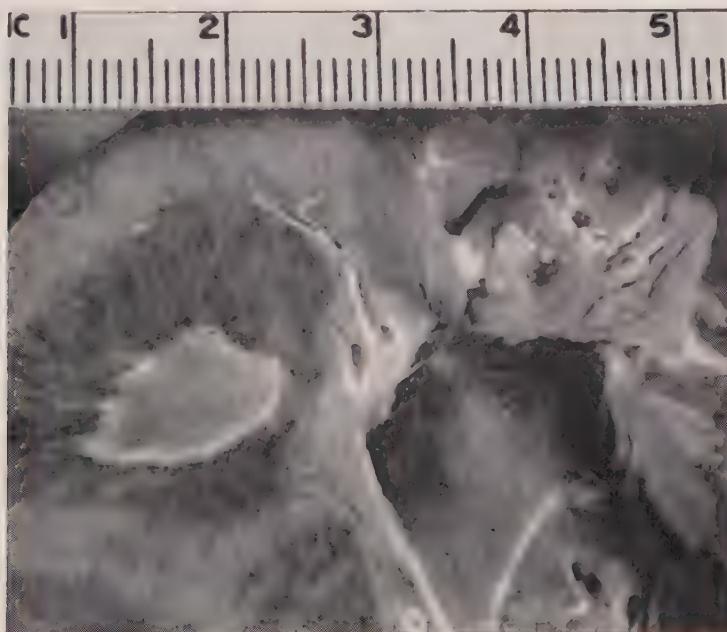


Fig. 465.—Papillary necrosis. The irregular outline of a necrotic area at the tip of a papilla can be seen at the left, and sequestration of a necrotic papilla at the right.

been reported in some such cases, many failures also have occurred, and some students of renal disease have concluded that pyelonephritis is seldom the cause of hypertension.

Pyonephrosis.—When an obstructive factor is added to pyelonephritis, hydronephrosis and hydronephrotic atrophy are also present in variable degree. When the distended hydronephrotic pelvis is filled with pus, the condition is referred to as pyonephrosis. The end result may be a thin-walled sac filled with pus.

The papillary necrosis is usually bilateral. The necrotic papillae stand out as pale grayish-yellow infarctlike areas bordered above by a reddish zone of inflammatory reaction. Usually all papillae appear grossly to be involved. In early stages there are small abscesses in the renal pyramid, at a level about two-thirds of the way from the tip of the papilla to the junction of the pyramid and cortex. These abscesses become confluent, and result in complete necrosis of the distal two-thirds of the pyramid. The cortex of the kidney shows in varying degrees the usual picture of acute pyelonephritis. Sequestration of the necrotic papillae occurs, and

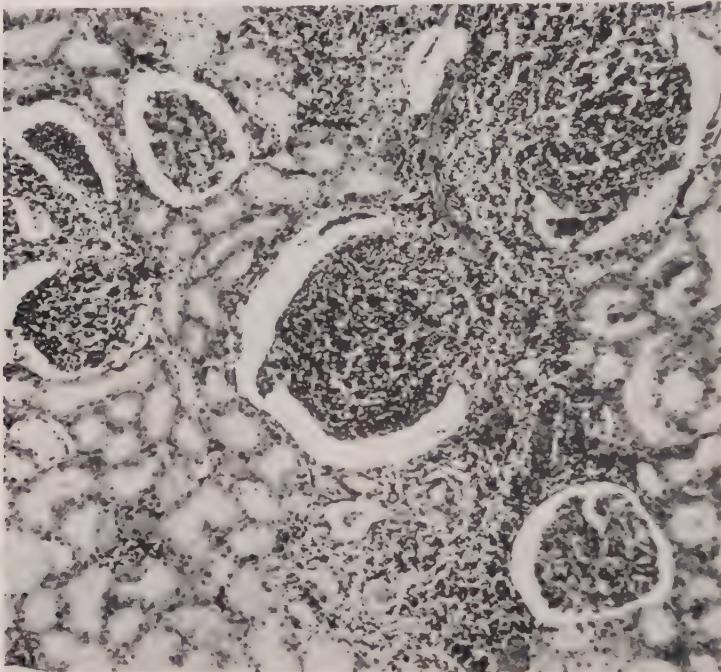


Fig. 466.—Focal syphilitic nephritis (Rich). Nodular accumulations of chronic inflammatory cells protrude into tubular lumina. (AFIP No. 79174.)

Necrosis of Renal Papillae (Necrotizing Renal Papillitis).—An unusual form of acute pyelonephritis distinguished by necrosis of the renal papillae occurs particularly in diabetic individuals over 40 years of age. Less commonly it complicates pyelonephritis in nondiabetic patients with urinary obstruction, most often due to prostatic enlargement.

Acute pyelonephritis is a fairly frequent complication of diabetes and in one series of autopsies on diabetes mellitus, about 25 per cent of those with acute pyelonephritis showed necrosis of renal papillae. The infection may involve the kidney from a focus elsewhere in the body, or may be confined to the urinary tract. In some cases the condition follows a fulminating course, uremia being present with or without diabetic acidosis, and death occurs within a few days. *Escherichia coli* and *Staphylococcus aureus* are the most commonly associated organisms.

the necrotic material, in late stages, is sloughed away. There is evidence that in rare cases healing may follow elimination of the necrotic papillae.

Microscopically, masses of bacteria are usually prominent in the necrotic pyramidal tissue. The zone of inflammatory reaction at the junction of necrotic and surrounding tissue may show surprisingly few neutrophilic leukocytes, but plasma cells may be unusually prominent. The central portions of involved papillae show necrosis, with pyknosis or loss of nuclei, maintenance of recognizable architecture, and relatively little or no inflammatory infiltration.

The mechanism of development of the lesion is probably by ischemia of the papillae, which ordinarily have a poor blood supply in comparison with the remainder of the kidney. Vascular changes of arterial and arteriolar sclerosis or intercapillary glomerulosclerosis are almost always present. The diabetic state itself is

clearly important, as apparently only in diabetics does the lesion develop in the absence of urinary tract obstruction.

Criteria for diagnosis of papillary necrosis in diabetic patients have been given as hematuria, renal colic, unexplained coma, and sudden increase in the severity of symptoms of a known pyelonephritis. Retrograde pyelograms may be helpful in diagnosis.

Syphilitic Nephritis.—Rich has described renal changes associated with syphilis, characterized grossly by tiny glistening grayish-yellow flecks and streaks of the cortex, and microscopically by focal interstitial accumulation of mononuclear cells, mainly lymphocytes. These nodular masses encroach upon cortical tubules, project into them, and often narrow the lumina. Crystals, or cleftlike spaces left by dissolution of crystals, are found in adjacent tubules. Spirochetes were not demonstrated in these lesions.

tuberculosis also occurs, in which there is a chronic ulcerative and spreading lesion. This form is usually unilateral, and the primary focus from which spread occurred often is not prominent. Embolic masses of organisms arrested in the kidney produce the first lesion in the cortex. By discharge of this lesion into a tubule, spread occurs to the medulla, where a caseous ulcerative tubercle appears on a renal papilla. From there spread occurs to the mucosa of the pelvis, ureter, and bladder. Reinfestation and extension to other portions of the kidney readily follow. Tuberculous strictures of the ureter and individual calices lead to stasis of urine and hydronephrotic changes. There

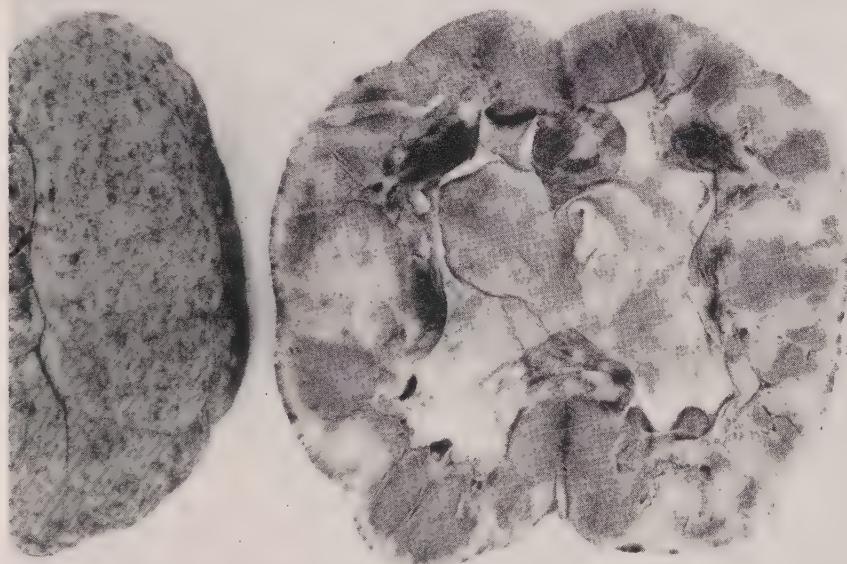


Fig. 467.—Leukemic infiltration of the kidney. The pale areas, predominantly in the cortex, are areas of massive accumulation of leukemic cells.

Syphilis has also been described as producing clinical findings similar to those of lipid nephrosis, although the underlying pathologic changes are not clear. Gumma of the kidney occurs but is very rare.

Tuberculosis of the Kidney.—Renal tuberculosis is secondary to an active tuberculous lesion elsewhere, the organisms reaching the kidney by hematogenous spread. The kidneys are usually involved along with other organs in acute miliary tuberculosis, but another form of renal

is progression of the tuberculous process in the kidney tissue through the stages of caseation, loss of tissue through ulceration, and hydronephrosis.

The appearance of the kidney depends upon the stage of the process. In an early period a few yellowish opaque tubercles are seen in the cortex and near the tip of a papilla. Later, caseous masses of varying size replace the renal tissue, and the ragged hydronephrotic cavities contain a thick creamy pus.

The infected ureter becomes thick-walled, rigid, and stenosed. The bladder involvement begins at the ureteral opening and spreads as an irregular area of ulceration. The lesions of the ureter and bladder tend to heal if the infected kidney is removed.

The Kidneys in Leukemia.—The kidneys are a common site for extensive infiltration of leukemic cells, particularly in chronic lymphoid leukemia. The kidneys are large and pale, and areas of very massive leukemic infiltration may

Miscellaneous Renal Lesions of Toxic and Metabolic Origin

HYPERPARATHYROID RENAL DISEASE

Renal Hyperparathyroidism.—Deficiency of renal function stimulates hyperplasia and hyperfunction of the parathyroid glands. The actual stimulating factor is probably some disturbance of calcium or phosphorus balance resulting from renal deficiency (see also page 1024). Parathyroid hyperplasia and

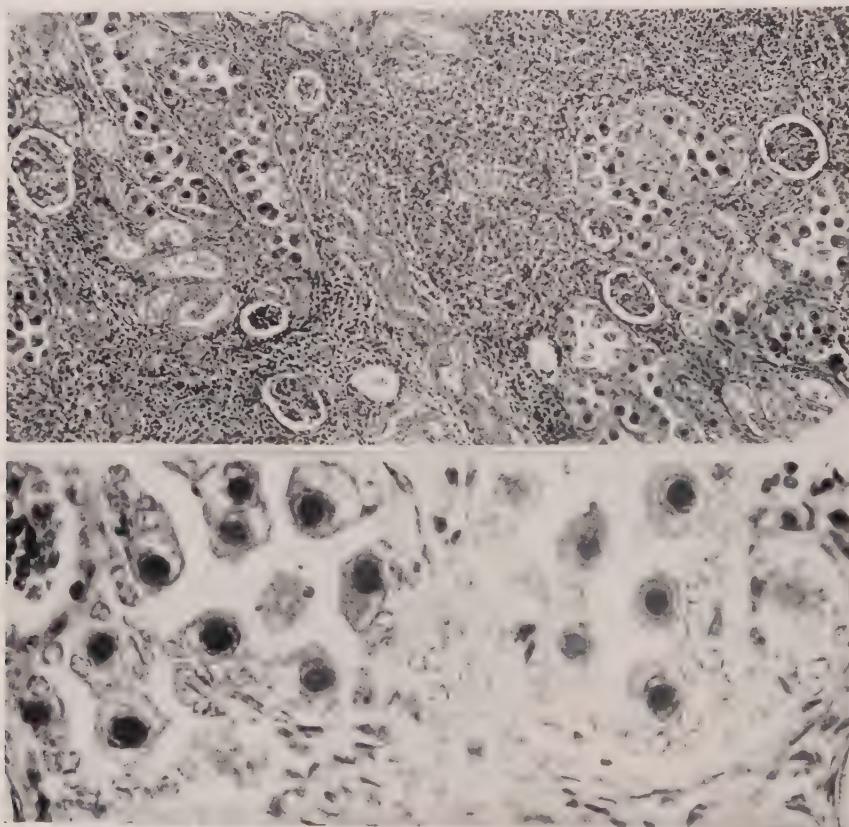


Fig. 468.—Inclusion disease of infancy. Prominent intranuclear inclusions are seen in tubular epithelial cells.

be evident as irregular, poorly circumscribed whitish areas of the cortex, evident on both the outer and cut surfaces. Hemorrhage into the pelvic and peripelvic tissues is common. Microscopically, the leukemic cells are seen infiltrating the interstitial tissues and replacing or crowding out the parenchyma. The tubules often seem more extensively replaced than the glomeruli. In some cases there may be confusion with acute interstitial nephritis, but in leukemia there is little variation in the type of infiltrating cells, almost all being monotonously of myeloid or lymphoid type.

hyperfunction are present in some degree in all cases having marked deficiency of renal function. If the disturbance is severe and long-continued, a clinical picture is produced similar to osteitis fibrosa cystica or renal rickets (in children).

Parathyroid Nephritis.—Hyperparathyroidism itself may produce renal lesions of a distinctive type and result in renal failure. The parathyroid hyperfunction may be due to a local

ized adenomatous overgrowth of a single parathyroid or to a peculiar diffuse hypertrophy and hyperplasia of all the parathyroids. The resulting disturbance in calcium metabolism appears to be the main cause of the damage to the kidney. Calcium deposits in the kidney are the characteristic feature. In acute hyperparathyroidism the calcium may be mainly intratubular, but in chronic hyperparathyroidism it is interstitial and peritubular and is accompanied by interstitial fibrosis and cellular infiltration. In some cases there is a striking calcification of the tubular basement membranes. Renal calculus formation is very frequent and develops on the basis of a parenchymal calcium concretion. Hyperparathyroidism is, however, the underlying cause of only a very small proportion of renal calculi.

Renal Rickets.—Renal rickets (renal dwarfism, renal infantilism) is a condition arising before

neys or some abnormality of the lower urinary tract resulting in dilatation of ureters and hydronephrosis. In the other group the renal changes have commonly been called chronic interstitial nephritis. Here there is advanced glomerular hyalinization or destruction but with little evidence of antecedent glomerulonephritis, such as crescents in Bowman's capsule. The tubules may be dilated or may have largely disappeared, their place being taken by chronic inflammatory cells and fibrosis in interstitial tissues. Small amounts of calcium are often present in interstitial tissue. In such cases the picture is that of the end stage of chronic pyelonephritis or of a kidney damaged by chronic hyperparathyroidism. In some of these cases the changes are due to a metabolic disturbance or cystine diathesis and cystinuria, which results in marked interstitial nephritis and renal atrophy.



Fig. 469.—Chronic pyelonephritis and hyperparathyroid renal disease (case of parathyroid adenoma.) Black calculous masses are evident in the renal substance and in the pelvis.

puberty, in which a prolonged chronic renal insufficiency is associated with stunting of growth, skeletal deformities, and sometimes failure of sexual development. Common clinical features are polyuria, polydipsia, high blood phosphorus, nitrogen retention, and low blood pressure despite renal failure. Renal disease develops before bone growth is completed and gives rise to renal insufficiency continuing over a long period. The failure of renal function causes retention of phosphates. A high level of blood phosphorus is characteristic and, in turn, stimulates the parathyroids to hyperplasia and increased function. The bone lesions, particularly in those cases with marked deformities, are those of osteitis fibrosa cystica and are due to excess of parathyroid hormone. Excess phosphates excreted by way of the intestine may combine with ingested calcium to form unabsorbable salts. In this manner true calcium starvation is added to the picture. In such cases the blood calcium is low, there is failure of bone growth (dwarfism), and bone lesions more nearly resemble true rickets.

The actual lesions in the urinary tract can be divided into two groups. In one there are lesions of a congenital nature, either cystic kid-

RENAL DAMAGE DUE TO HYPER-VITAMINOSIS D

Unlike other vitamins, vitamin D when administered in great excess may cause damage to tissues. In experimental animals there occurs some skeletal decalcification and metastatic deposition of calcium in the kidneys and other tissues (lungs, blood vessels). Renal calculi may be formed. Tubular obstruction, destruction, and fibrosis occur in a fashion similar to the effects of parathyroid hormone injection. There is evidence of similar effects in rare cases of hypervitaminosis D in children and adults.

RENAL CALCULI

Stones or calculi formed in the urinary tract are due to precipitation of chemical salts in the urine. Calculi are frequently classified as primary and secondary. The primary stones are those formed without apparent causal factors, such as infection, inflammation, or urinary obstruction and

stasis. Secondary stones are those which follow evident inflammation or obstruction.

Etiology.—The several factors which may play a part in stone formation, singly or in combination, are:

1. *High concentration of crystalline salts in the urine* favors precipitation. Colloids in the urine hold the crystalloids in solution in a supersaturated state. The balance is delicate and easily disturbed either by hyperexcretion of crystalloids, such as may occur in hyperparathyroidism, or by decrease of colloids, which may be due to infection. The result is precipitation of the crystalline matter and colloids, the colloidal gel forming an organic framework.

mental production of stone. How important a factor this may be in man is still uncertain.

4. *Urinary reaction* is important in maintenance of urinary salts in solution and largely determines the composition of the stones. However, reaction alone, e.g., marked alkalinity, is probably never the cause of stone formation.

5. *Urinary obstruction* acts by promoting stagnation and infection. It is rarely the sole factor.

6. *Hyperparathyroidism* has a known direct relationship to renal stone formation but probably accounts for 1 per cent or less of renal calculi, although in some clinics up to 5 per cent have been ascribed to hyperparathyroidism. The greatly increased urinary excretion of calcium and phosphorus in the urine and the tendency to deposition of calcium salts in renal tissue result in calculus formation in 30 to 70 per cent of cases of hyperparathyroidism.



Fig. 470.—Renal calculus. Calcium plaque in tissue with attached early stone. Note the narrow necklike attachment of the calculus and its laminated structure due to successive deposits of precipitated material. (From J. Urol. 44: 29, 1940.)

2. *Encrustation of solid material with urinary salts* is a factor of importance. A nidus for such precipitation may be bacteria, necrotic or degenerated tissue, or other foreign bodies. The association of many calculi with bacterial infection has been proved. Randall has described the mechanism by which encrustation frequently occurs on a small calcified plaque of a renal papilla.

3. *Vitamin A deficiency*, known to produce changes in the epithelial lining of the upper urinary tract, has been effective in the experi-

Pathogenesis.—The mechanism of primary stone formation has been described by Randall. Damage to a renal papilla results in calcium deposit in the injured tissue. When near the surface, this plaque of calcium becomes exposed by ulceration of overlying tissue and becomes a nidus on which any urinary salt may crystallize. Successive depositions

produce a laminated stone, often of variable composition. The plaque holds the stone in place until it has time to reach a considerable size before tearing away from its moorings.

Types.—While most stones are composed of mixtures of uric acid, calcium oxalate, and ammonium-magnesium phosphate, certain constituents predominate and give the stone distinctive character. *Uric acid stones* are brown, fairly smooth, moderately hard, and on section show concentric lamination. *Oxalate* stones are

of obstruction may be in the renal pelvis, ureters, or bladder. Partial or intermittent obstruction gives rise to dilatation of ureter or renal pelvis (hydro-nephrosis) above the obstructed point. Stasis due to obstruction promotes infection (pyelonephritis). Passage of a small stone through the ureter produces the severe pain of renal colic.

RENAL LESIONS IN GOUT

Renal functional deficiency and high blood pressure are common in individuals who have



Fig. 471.—Calculous pyonephrosis. Renal calculus in dilated pelvis of kidney. (Courtesy Dr. H. C. Schmeisser.)

very hard, have a rough spiny surface of dark brown color, and are laminated. *Phosphate* stones are soft, smooth, white, and friable. Uric acid and oxalates tend to precipitate in an acid urine, while phosphate stones are commonly associated with alkaline urines.

Sulfapyridine administration may be associated with the formation of small stones, due to precipitation of acetylated sulfapyridine.

Effects.—Renal calculi may obstruct the outflow of urine, promote infection, and cause the pain of renal colic. The point

been prolonged sufferers from gout. While in some cases this is due to renal vascular disease or glomerulonephritis in gouty individuals, there also occur more specific renal lesions. These consist of the precipitation of urates in the collecting tubules of the medulla, with tubular obstruction, chronic inflammation, and fibrosis. Crystalline deposits may be found in the pyramids, or within the pelvis or ureters. The destruction and atrophy from gouty tophi in the pyramids may be sufficient to cause renal insufficiency.

URATE DEPOSITS (URIC ACID INFARCTS)

Deposits of urates are commonly seen in the medullary pyramids of newborn infants, or in the first few weeks of life, and also rarely in

adults. In the newborn the excess uric acid has been supposed to arise from the destruction of the nuclei of erythroblasts, and in adults from marked destruction of nucleoprotein in certain diseases such as leukemia and pneumonia. The rays of the medullary pyramids show opaque yellowish lines and masses. They are due to dilatation of the collecting tubules by masses of urate crystals. There is no inflammatory reaction, and, unless special precautions are taken in preparation of the tissues, the uric acid and urates are dissolved and little is to be seen on microscopic examination. Although the streaky yellowish opaque gross appearance of the pyramids has been termed "uric acid infarcts," they are not true infarcts in the usual sense of the term. There is no permanent damage of renal tissue (see Fig. 68, page 78).

renal failure. The kidneys in such cases are characterized by degenerative changes in the distal portions of the nephrons, and pigmented casts in the tubular lumina. While the pathogenesis of the renal lesion has not been completely elucidated, it appears to be on the basis of a disturbance of renal blood flow, in which hemoglobin or myoglobin and derived pigments may play a part in some cases.

Hemoglobinuric nephrosis is characteristically observed in cases of massive hemoglobinemia and hemoglobinuria, such as occurs in blackwater fever and after trans-

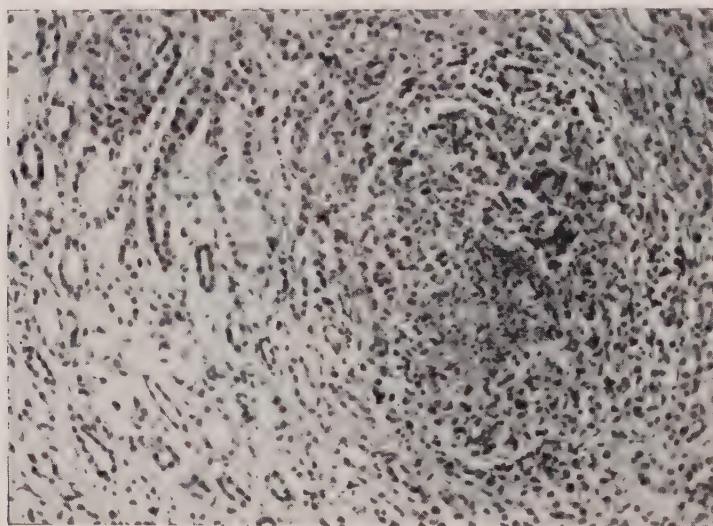


Fig. 472.—Focal necrotic lesion of kidney in sulfonamide poisoning.

RENAL DAMAGE DUE TO SULFONAMIDES

Sulfonamide drug therapy may result in two types of injury to the kidney: (1) precipitated sulfonamides and acetylated derivatives causing mechanical obstruction in the urinary tract, and (2) "nephrotoxic" lesions. The latter are focal or diffuse tubular degenerations and necrosis with intense inflammatory reactions in the interstitial tissue around the nephrons. Inflammatory reaction also may be prominent in the walls of small blood vessels. The nephrotoxic lesions appear to be independent of the amount of drug administered and of mechanical blocking by precipitates, and may have an allergic basis.

HEMOGLOBINURIC NEPHROSIS (LOWER NEPHRON NEPHROSIS)

A variety of conditions in which there occurs a fairly massive destruction of blood or tissues and shock may be followed by oliguria or anuria, and death from

fusion with incompatible blood. Severe traumatic injuries involving crushing of muscular tissues or prolonged muscular ischemia also produces the condition; and it was a prominent sequel of injuries in World War II (crush syndrome; post-traumatic anuria). Similar renal lesions occur in some cases of severe burns, heat stroke, uteroplacental damage, sulfonamide intoxication, and after certain poisons. Shock and excessive vomiting are often associated with the conditions leading to hemoglobinuric nephrosis. The development of renal functional failure is associated with oliguria, which often progresses to anuria. The urine excreted is highly acid, gives a positive benzidine reaction, and shows pigmented material or pigmented casts on microscopic examination.

The gross appearance of the kidneys is not specific. There are usually some swelling and enlargement, with increase of weight. The outer and cut surfaces of

volving focal portions of the distal part of Henle's loop and distal convoluted tubules. The interstitial tissue around these damaged areas shows edema and cellular

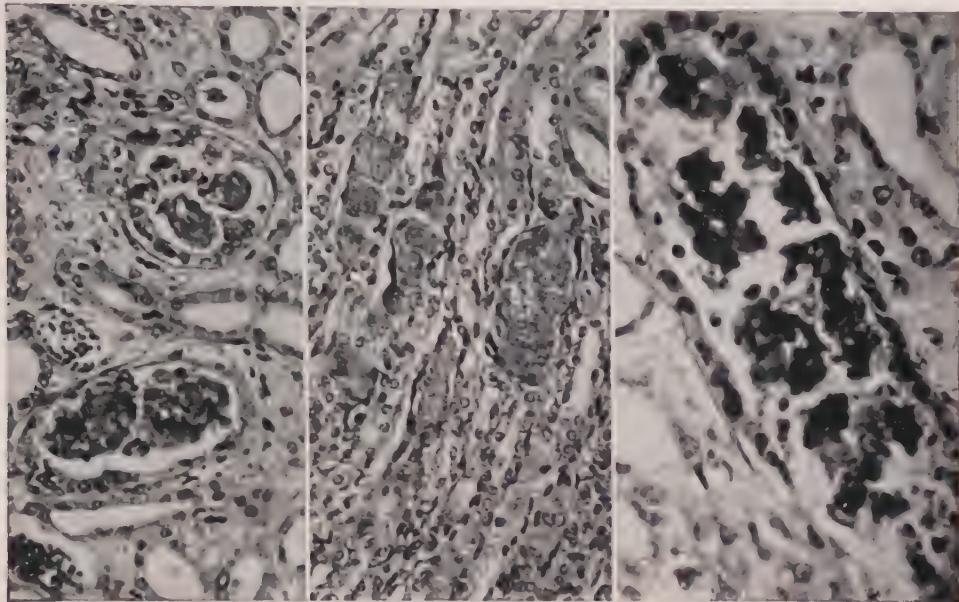


Fig. 473.—Hemoglobinuric nephrosis due to transfusion reaction. The tubules contain pigment casts and the epithelial lining cells show degenerative changes.

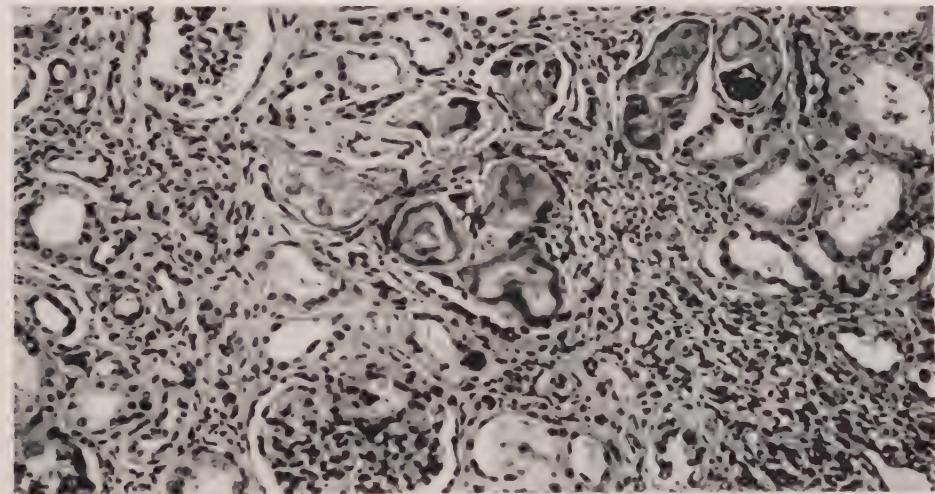


Fig. 474.—Kidney from a case of multiple myeloma, showing characteristic casts. There is chronic interstitial inflammation and early atrophy of tubules. (AFIP No. 86999.)

the cortex are pale, but the medulla is dark or dusky and shows accentuated striations.

The microscopic changes are characterized by degeneration and necrosis in-

filtration, often with thrombosis of adjacent veins. Reddish or brownish casts of a heme compound are found in the lumina of the distal tubular segments and in the collecting tubules. The glomeruli

and proximal convoluted tubules show relatively slight or no changes. The oliguria or anuria may be mainly due to disturbance in renal circulation with inadequate glomerular filtration and contributed to by the blockage of tubular lumina with pigment casts, and by excessive reabsorption or leakage of glomerular filtrate through the damaged tubular walls (see also Fig. 92, page 130).

The pathogenesis of the renal lesion is not completely established, but much evidence suggests that it has a vascular basis, with disturbance of renal blood flow and ischemia. A renal vasomotor mechanism has been demonstrated which on stimulation causes renal cortical ischemia and diverts blood flow to the medulla. Hemoglobin and derived pigments may play some part in producing this vascular disturbance, in addition to the effect of tubular blockage.

RENAL DAMAGE WITH MULTIPLE MYELOMA

The occurrence of Bence-Jones proteinuria in association with multiple myeloma (see page 1241) may be associated with considerable renal injury, particularly if the excretion of the Bence-Jones protein is in considerable quantity and the duration is prolonged. The Bence-Jones protein appears to have no specific toxic effect upon renal parenchymal cells, but the injury is due to precipitation of the protein in the tubules. Casts of the precipitated material completely obstruct tubular lumina, persist, and provoke a foreign body reaction, and lead to atrophy of affected nephrons. In rare prolonged cases, considerable renal atrophy may develop, with renal insufficiency, and the kidneys are found to be small and granular.

THE KIDNEYS IN TOXEMIA OF PREGNANCY

Renal lesions regularly accompany the toxemias of late pregnancy (eclampsia, pre-eclampsia, etc.). The glomeruli are enlarged, bloodless, and have narrowed capillaries. Most of the capillary narrowing is accounted for by marked thickening of the basement membrane of the tufts. Tubular changes are constantly present and often are more prominent than glomerular lesions. The convoluted tubules, particularly, are involved by changes which vary from mild cloudy swelling or fatty degeneration to hyaline droplet degeneration and even necrosis. The tubular changes, although more striking, are probably secondary and of less real importance than the glomerular lesions. The lesion characterized by ischemic glomeruli with diffusely and uniformly thickened basement membranes is considered a distinctive variety of membranous glomerulonephritis.

Glomerular edema and vacuolation have been considered by some to be the important feature.

In some cases of pregnancy toxemia, the renal changes are those of primary glomerulonephritis, pyelonephritis, or hypertensive arteriolar nephrosclerosis. More than half of the women who recover from eclampsia eventually develop hypertensive cardiovascular renal disease. The rare bilateral renal cortical necrosis also may occur in association with pregnancy.

Hydronephrosis

Hydronephrosis is a dilatation of the renal pelvis and associated atrophy of renal tissue resulting from an obstruction to the outflow of urine. Including mild as well as severe degrees, this is one of the commonest of renal lesions. The obstruction may be due to a great variety of causes, including urethral stricture, prostatic enlargements, tumors or inflammations of the bladder, pregnancy, tumors of the uterus, ovaries, or other pelvic structures, renal calculi, ureteral strictures, and congenital abnormalities causing stenosis in some part of the urinary tract. In some cases there is no mechanical obstruction, but back pressure is produced because of paralysis of the bladder or interference with ureteral function as a result of spinal cord injury or disease. In rare cases there is a congenital hydronephrosis and hydroureter in which neither mechanical nor functional obstruction is demonstrable.

Urine is forced out of the renal pelvis and down the ureter by waves of active contraction. When obstruction causes increase in intrapelvic pressure to rise above the effective glomerular filtration pressure (glomerular capillary blood pressure less osmotic filtration pressure), formation of a glomerular filtrate and tubular function cease, and a disuse atrophy occurs. A simple atrophy of the kidney without any marked degree of pelvic dilatation occurs in some cases of sudden, complete, and permanent obstruction of a ureter. However, most causes of obstruction in the urinary tract are more gradual in their development, or are intermittent or incomplete. In such cases, loss of function of nephrons and atrophy of the renal parenchyma occurs more gradually, and is accompanied by a greater amount of pelvic dilatation. Mechanisms which may be effective in decreasing intrapelvic pressure and hence allowing glomerular filtration to continue have been demonstrated. With increased intrapelvic pressure, material from the pelvis appears in renal veins (pyelovenous backflow). A reflux by way of collecting tubules (pyelotubular backflow) and also into lymphatics has been described. How important these reflux mechanisms may be in the usual case of hydronephrosis is a matter of some debate.



Fig. 475.—Hydronephrosis due to obstruction of the upper end of ureter. (Courtesy Dr. H. C. Schmeisser.)

The site of obstruction in the urinary tract influences the findings in hydronephrosis. An obstruction of the urethra due to prostatic enlargement produces bilateral hydronephrosis and dilated ureters. The most extreme degrees of hydronephrosis are unilateral and due to ureteral obstruction. The unaffected kidney may exhibit a compensatory hypertrophy. A mild degree of hydronephrosis, particularly of the right kidney, occurs in the later months of pregnancy in almost all cases. Stricture of the ureter at its upper end (ureteropelvic junction) may be found as a cause of hydronephrosis in either children or adults, and when unilateral may produce extreme degrees of hydronephrosis. Occasionally, an accessory renal artery to the lower pole of the kidney presses upon the upper end of the ureter with obstruction as a result.

With distention of the renal pelvis the calyces flatten, the renal tissue becomes atrophic and thin, and the dilated pelvis assumes a saccular and rounded form. In severe cases the total size of the kidney and pelvis may be increased, and the outer surface lobulated. Eventually, only a thin



Fig. 476.—Hydronephrotic atrophy of kidney. Full thickness of renal substance with pelvic mucosa below at right.

shell of renal parenchyma may remain. The atrophy, fibrosis, and disappearance of renal parenchyma appear to affect tubules more rapidly than glomeruli.



Fig. 477.—Calculus in ureter, with hydroureter, hydronephrosis, and pyelonephritis. (Courtesy Dr. S. B. Pessin.)

Hence, except in late stages, the tubular atrophy may seem to be out of proportion to the glomerular change. This disproportionate loss of tubules, leaving many glomeruli seemingly intact with relatively few tubules, may be very striking. Eventually the glomeruli become converted into rounded hyalinized masses and disappear. The amount of atrophy and change in the renal parenchyma depends on the duration and degree of the hydronephrosis. In mild bilateral hydronephrosis there may be little change in the renal parenchyma.

In some cases a great part of the pelvic dilation is outside the kidney (extrarenal

pelvis) and a large hydronephrotic sac forms at the hilum of the kidney.

Very many cases of urinary tract obstruction are complicated by infection, the hydronephrotic changes having the addition of those due to pyelonephritis or pyonephrosis.

Congenital Malformations and Anomalies

Renal Agenesis and Hypoplasia.—A bilateral congenital absence or hypoplasia of the kidneys is rare and incompatible with life. The infants with renal agenesis are usually premature. Hypoplasia of the lungs is usually present. Potter has described a characteristic facial appearance in these infants due to increased space between the eyes, a prominent inner canthal fold, flattening of the nose, recession of the chin, and large, low-lying ears. Other congenital abnormalities are frequently but not invariably present, particularly absence of the uterus and vagina in female infants.

Unilateral renal agenesis is more common than bilateral, and is slightly more frequent on the left side and in males. The opposite solitary kidney is larger than normal and occasionally its weight may be equal to that of two normal kidneys. The ureter of the absent kidney is usually lacking, although remnants sometimes may be found. Arrested development of the mesonephron appears to be the basis of renal agenesis.

Unilateral congenital renal hypoplasia is less common than unilateral acquired atrophy of one kidney as a result of interstitial nephritis, obstruction, or vascular disease.

Congenital fusion of the kidneys is most commonly a connection of the lower poles, either by a fibrous band or by actual renal tissue (**horseshoe kidneys**). The pelves are separate, and the ureters pass anteriorly across the lower poles of the kidneys.

Duplication of ureters, double pelvis, or both, are common anomalies, usually of no functional significance. Persistence of some degree of fetal lobulation of the kidneys is also very common and harmless.

CYSTS OF THE KIDNEY

Cysts of the kidney are of three main types: *solitary cysts*, *retention cysts*, due to tubular dilatation in vascular or inflammatory disease of the kidney, and the condition of *congenital polycystic kidneys*. A fourth variety, *peripelvic lymphatic cysts*, is rare.

The solitary cysts are usually serous, but they may be hemorrhagic. They vary from a few millimeters to several centimeters in diameter. Some are congenital in origin and others result from tubular obstruction. Occasionally they are multilocular.

In advanced renal vascular disease or glomerulonephritis there frequently are

multiple small cysts, usually only a few millimeters in diameter, resulting from tubular dilatation.

Peripelvic lymphatic cysts of the kidney are lymphatic distentions associated with obstruction of the lymphatic trunks of the hilus of the kidney. They are usually small and unimportant, but rarely have caused damage by pressure on renal vessels.

Congenital Cystic Kidney.—Congenital polycystic kidney is an hereditary maldevelopment. One or both kidneys may be involved by extremely numerous cysts of varying and often large size. The condition is present at birth, and absence of

Other cases simply present acute or chronic renal failure, with mild hypertension and cardiac hypertrophy, so that clinical differentiation from other types of renal disease may be very difficult. Attacks of hematuria are a quite distinctive finding and are due to rupture of blood vessels into cysts communicating with the pelvis.

The involved kidneys may be moderately or enormously enlarged. Enlargement is due to increase in size of individual cysts, rather than to increase in their number. The kidneys have a knobby or irregular outline. The cysts are lined by cuboidal

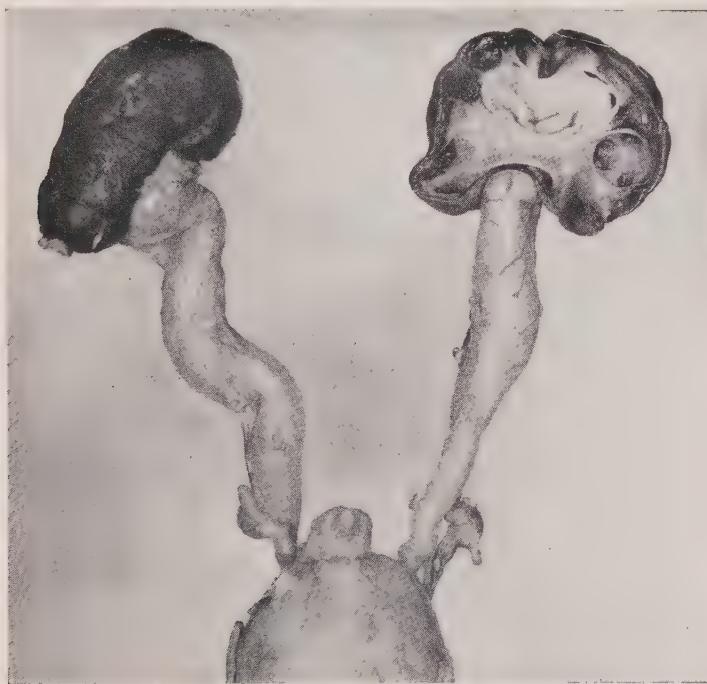


Fig. 478.—Congenital hydronephrosis. (Courtesy Dr. S. B. Pessin.)

sufficient functioning renal tissue may result in death at that time or within the next few years. If renal functional tissue is sufficient, life may go on with little or no clinical evidence of the disease until the third, fourth, or fifth decade. At that time renal failure results from the development of vascular disease, other accumulated injuries of the kidney, or progressive increase in the size of the cysts. The patient may have lumbar pain, tumor mass in the kidney region, and hematuria, a picture simulating renal neoplasm.

or (more commonly) flattened epithelium. In the newborn group the remaining renal tissue is hypoplastic, the number of nephrons being reduced and interstitial connective tissue excessive.

At a later age, in cases without clinical symptoms, the functional renal tissue between cysts is often abundant. The patients dying of renal failure show extreme atrophy of the renal tissue between cysts, due to progressive cystic enlargement and associated development of arterial disease.



Fig. 479.—Solitary cyst of kidney. (Courtesy Dr. H. C. Schmeisser.)

The origin of the condition is related to the manner of embryologic formation of the kidney. The kidney is developed from two separate portions which must join. The one portion, from metanephric blastema, forms convoluted tubules and glomeruli. The other portion, from the Wolffian duct, forms ureter, renal pelvis, and collecting tubules. "Failure of union" of collecting ducts with convoluted tubules has long been supposed to give rise to the cystic change. Kampmeier has pointed out another possible origin. He showed that the uriniferous tubules, particularly of the first but sometimes of later generations, fail to gain reattachment to collecting ducts. They then undergo cystic dilatation but later normally disappear. If instead of disappearing they continue to grow and expand, polycystic kidney results. Other abnormalities of the genitourinary tract or congenital cysts of liver or pancreas are often present in individuals with polycystic kidneys.

Tumors of the Kidney

Renal neoplasms of clinical importance do not form a large or frequent group of tumors, but they include interesting tumors of peculiar structure and distinctive occurrence. There has been a great deal of study and controversy concerning their origin and nature. Benign renal tumors include hamartomas, adenomas, fibromas, lipomas, leiomyomas, and hemangiomas. They occur with greater frequency than malignant tumors, but usually are seen as but incidental findings, and but a small proportion give rise to clinical disturbances. Malignant renal tumors as a group, although less numerous, are associated with a poor outlook and a high

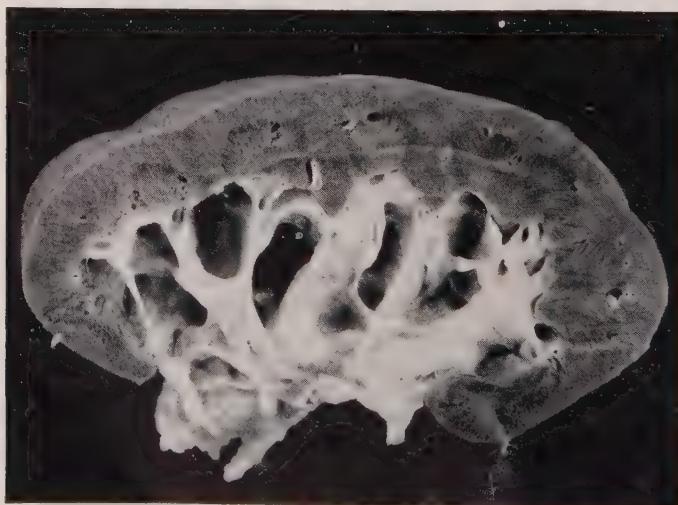


Fig. 480.—Peripelvic cysts of the kidney. (Courtesy Dr. J. F. Kuzma. From Anderson, Synopsis of Pathology.)

mortality. This is due not so much to a high degree of inherent malignancy as to the infrequency of clinical diagnosis and removal before relatively advanced stages. Malignant renal neoplasms are of four types: adenocarcinomas (hypernephromas), embryomas (Wilms' tumors), carcinomas of the renal pelvis, and sarcomas.

in diameter, in the medulla of the kidney or sometimes in the cortex. They are not encapsulated and may be indistinctly separated from adjacent renal parenchyma. Microscopically, they are composed of irregular bundles of smooth muscle and connective tissue fibers, and occasionally some fatty tissue.

Similar areas of developmental tissue disturbance assuming a tumorlike appearance are found in the majority of cases of tuberous

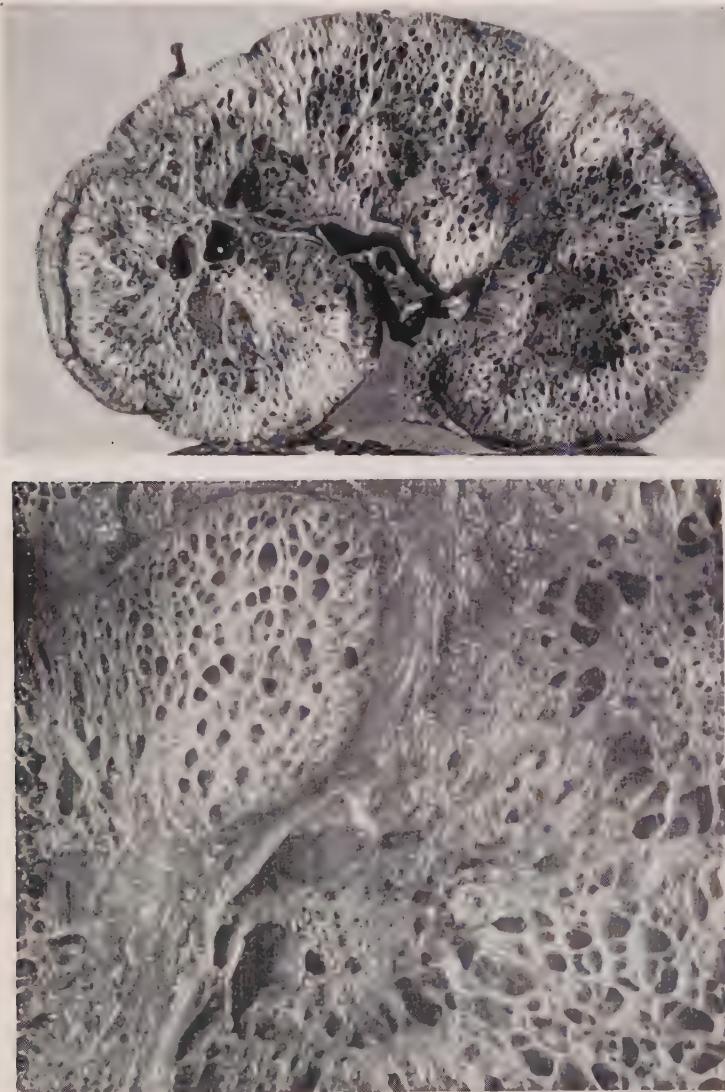


Fig. 481.—Congenital cystic kidney, newborn infant. The lower figure shows a magnification of the cut surface.

BENIGN RENAL TUMORS

Hamartoma.—Probably representing an anomaly of development rather than a true neoplasm, hamartomas are seen as small rounded grayish nodules, usually only a few millimeters

sclerosis. The tumors are often multiple and bilateral, and may be composed of fatty tissue, fibrous tissue, smooth muscle, small blood vessels, or mixtures of these various tissues. The tumors may reach a size of several centimeters, but almost invariably remain benign.

Adenoma.—Adenomas are quite commonly seen as small grayish tumors in the outer parts of the cortex of the kidney. They vary from a few millimeters up to two or three centimeters

age. Microscopically, they are composed of dark-staining epithelial cells forming tubular and cystic structures into which there are irregular papillary projections. In some cases the project-

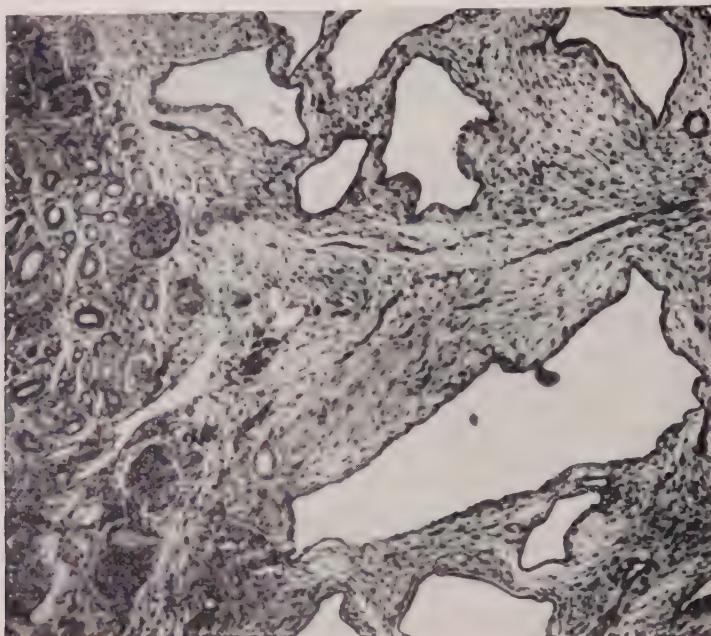


Fig. 482.—Congenital cystic kidney, newborn infant. Cystic spaces are surrounded by an embryonic type of connective tissue. Clomeruli and tubules are evident on the left.

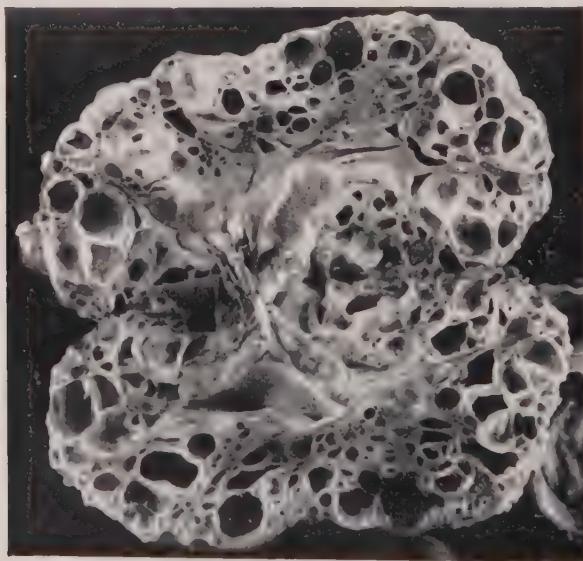


Fig. 483.—Polycystic kidney of an adult.

in diameter. The majority have a papillary cystadenomatous architecture, are often multiple, and are incidental findings in scarred or nephrosclerotic kidneys of individuals past middle

age. Such tumors have been thought to be of metanephric origin, and for them the term "glomeruloma" has been proposed. Renal ade-

nomas of similar histologic structure are not uncommon in swine and rabbits.

Solid adenomas found in the renal cortex are composed of sheets or cords of small dark-staining cells, or cells with pale clear or granular cytoplasm. Their histologic structure is similar to that of many renal adenocarcinomas. Bell has suggested that they are merely early stages of malignant renal carcinomas, but arbitrarily classifies all tumors of this type which are less than 3 cm. in diameter as adenomas, because metastases are rarely found except when such tumors are of larger size.

Fibroma.—Most of the so-called fibromas of the renal medulla are probably hamartomas. However, small subcapsular fibromas also occur, and rare larger fibromas up to 10 cm. and more in diameter have been described.

to the fatty tissue variable amounts of connective tissue, smooth muscle, myxomatous vascular tissue, and cartilage. In rare cases there are areas which histologically suggest a sarcomatous change (liposarcoma), but metastases from such tumors have not been reported.

Primary intrarenal lipoma must be distinguished from fatty replacement of destroyed renal parenchyma, from perirenal lipomatosis, and from perirenal lipoma. Replacement of destroyed renal parenchyma by fatty tissue (renal lipomatosis) is not particularly rare. It may occur as a result of any process which destroys renal tissue, and has no causal relationship with any specific inflammation. It is seen particularly in pyelonephritis and calculous pyonephrosis. In most it is an increase of adipose tissue about the pelvis and also of the perirenal tissue, replacing and encroaching upon atrophied

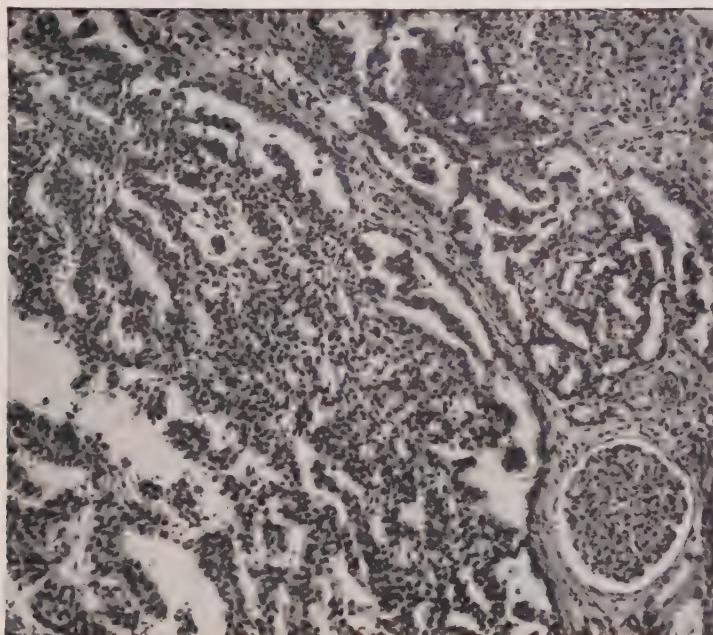


Fig. 484.—Benign adenoma of kidney. The edge of the tumor is shown, with glomeruli of the adjacent renal tissue on the right.

Leiomyoma.—Small subcapsular leiomyomas are not uncommon as incidental postmortem findings. They are usually well circumscribed, only a few millimeters in diameter, and probably develop from smooth muscle of the capsule. Rare cases of larger leiomyomas or malignant change in a leiomyoma have been described.

Lipoma.—Small intrarenal lipomas composed of fatty tissue of adult type are uncommon, but are sometimes seen as incidental postmortem findings. A few cases have been reported of benign intrarenal lipomas which reached a large size, gave clinical evidence of their presence, and were difficult to differentiate from renal cancer. They appear to begin in a cortical or subcapsular position, and may contain in addition

renal parenchyma. In some cases the kidney and associated adipose tissue may reach a very large size.

Perirenal lipoma arises from perinephric fat and may contain considerable admixture of fibrous and myxomatous tissue. As it attains larger size, it is difficult to distinguish from other retroperitoneal lipomas. Sarcomatous change may occur.

Hemangioma.—Hemangiomas of the kidney are rare, but may give rise to hematuria of moderate or severe degree. They are benign, and usually of the cavernous type. They may be associated with hemangiomatosis of the skin or other organs.



Fig. 485A.—Fibroma in medulla of kidney. (From Anderson, Synopsis of Pathology.)

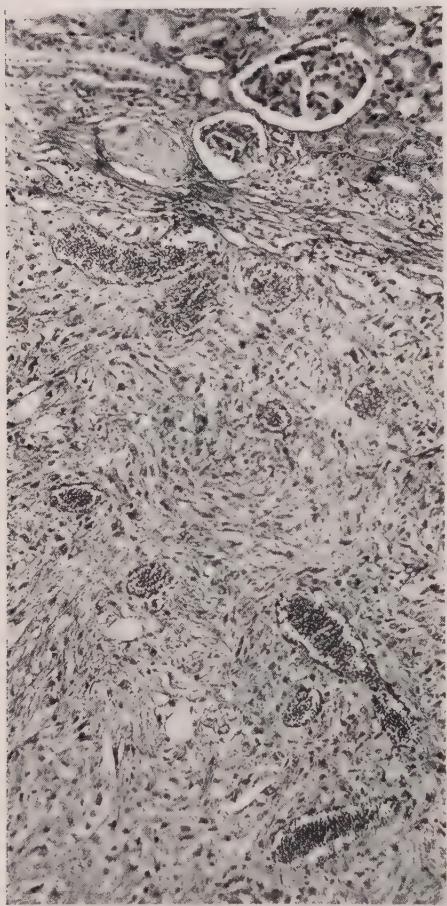


Fig. 485B.—Fibroma of the kidney. Glomeruli and tubules are evident at the top.

MALIGNANT RENAL TUMORS

Adenocarcinoma of the Kidney.—Adenocarcinomas of the kidney occur almost always in individuals past the age of

40 years, with a peak incidence in the sixth and seventh decades. The frequency in males is more than twice that in females. About 80 to 90 per cent of malignant tumors of the kidney belong in this group.

The terminology used for these tumors is variable, and varieties are referred to as Grawitz tumors, hypernephromas, hypernephroid tumors, clear-cell carcinomas, renal cell carcinomas, etc. While variations in histologic structure have been used to make such distinctions, as great a histologic variation is often present in different areas of a single tumor, and the current tendency is to call them all either carcinomas of the kidney or hypernephromas.

The term hypernephroma originated from the theory of Grawitz, who in 1883 published evidence that they arose from "rests" of adrenal cortical cells in the kidney. Small areas of adrenal cortical tissue are often found in the outer part of the kidney, just beneath the capsule. Adrenal heterotopia, with all or part of the adrenals within the capsule of the kidneys, is sometimes encountered. Also adrenal tissue is not uncommon on the undersurface of the liver and in internal genitalia. Further evidence of the adrenal nature of these tumors lies in their close microscopic resemblance to adrenal cortex. They are composed of large clear cells showing hydropic changes or containing abundant doubly refractive cholesterol esters, and the cells may be arranged in cords as in the adrenal cortex. However, this evidence is insufficient proof of their adrenal origin. Hypernephromas never give rise to the endocrine and sexual disturbances that accompany true adrenal cortical tumors. Tumors of similar histologic appearance may be found in tissues other than the adrenal, such as salivary glands (see page 754 and Fig. 670). Some areas of the tumor may show a papillary or tubular structure, and all gradations may be found between a close resemblance to adrenal cortex, and clear-cut renal carcinoma. Hence hypernephromas are generally considered to be simply renal carcinomas. However, attempts have been made to reconcile the evidences of adrenal and renal origins by suggesting that the tumor arises from cells retaining early embryonic potentialities for differentiation into either type of tissue.



Fig. 486.—Hypernephroma (Gräroitz tumor) of the kidney.

The hypernephroma forms a large rounded tumor in the kidney, at first well encapsulated and separated from the renal tissue. It is microscopically invasive, however, so that it is not easily shelled out or separated from surrounding tissue. The yellowish cut surface shows some connective tissue trabeculae coursing irregularly through the tumor. There is a marked tendency to degeneration, necrosis, hemorrhage, and cyst formation. Microscopically, the characteristic cells are large, with abundant, pale, foamy cytoplasm. In some areas the cells may be smaller, with a denser, slightly granular, and more eosinophilic cytoplasm, more like ordinary renal tubular epithelium. The cells are arranged in solid sheets, or as cords and papillary structures with a thin supporting stroma.

The growth of the tumor causes atrophy and fibrosis of adjacent tissue. In later stages there is extensive invasion of renal substance. The tumor cells have a tendency to invade and grow along blood vessels. Metastasis occurs by blood stream, and the lungs and bones are the common sites for the secondary tumors.

Because of the relatively localized growth of hypernephroma in its early stages, it may attain considerable size with only

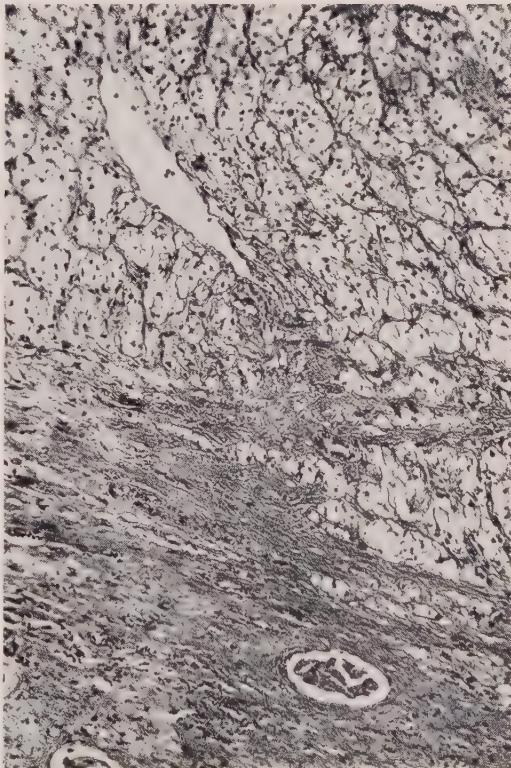


Fig. 487.—Hypernephroma of the kidney. Compressed atrophic renal substance is seen at the bottom.

painless hematuria as clinical evidence of its presence. Metastases in lungs or bones may be the first indication.



Fig. 488.—Wilms' tumor of kidney. In this relatively early stage it appears well encapsulated and sharply separated from the renal tissue. (Courtesy Dr. H. C. Schmeisser.)

Embryoma.—Wilms' tumor or embryonal adenocarcinoma is a rare mixed tumor of the kidney, the occurrence of which is practically limited to the first seven years of life, although a few cases have been reported in adults. The average age is 3 years. These tumors account for about 20 per cent of all malignancies in childhood. The origin is believed to be from mesodermal cells displaced during development but retaining the ability to grow and differentiate into various types of tissue. Being rapidly growing tumors of embryonic nature, they are highly radiosensitive.

At first the tumor is surrounded by a dense connective tissue capsule and remains separated from the renal parenchyma until quite large. The kidney tissue is pushed into various shapes. Eventually the capsule is ruptured and extension occurs to kidney tissue, omentum, and adjacent viscera. Blood-borne metastases are common in lungs and brain, but liver and regional lymph nodes are also frequently involved.

The tumor tissue is uniformly grayish-white and moderately firm, but cysts or hemorrhage may be present. Microscopically, the predominant tumor elements are an abundant embryonic type of malignant connective tissue surrounding some

glandlike tubules of variable size and shape. Epithelial cells may also form solid cords and strands of cells. A rosette-like arrangement of epithelial cells is occasionally seen. Sometimes there are structures resembling abortive glomeruli. Occasionally, smooth or striated muscle, cartilage, or myxomatous tissue is present.

Tumors of the Renal Pelvis.—The pelvis of the kidney gives rise to the same types of tumor as are found in the urinary bladder, the common forms being papillomas and papillary carcinomas. Infiltrating forms also occur, which may extend into the renal substance. A rare form is a squamous cell carcinoma, which may be papillary, or may be infiltrative and extend early into the renal parenchyma. There may be an associated leukoplakia of the renal pelvis or the presence of renal calculi. Early and widespread metastasis tends to occur, and the prognosis is poor.

Sarcoma.—Sarcomas of the kidney are rare, apart from the undifferentiated or



Fig. 489.—Wilms' tumor of kidney. Note the tubular or rosette-like structures amidst the tissue of sarcomatous appearance.



Fig. 490.—Papillary carcinoma of renal pelvis. (Courtesy Dr. H. C. Schmeisser.)

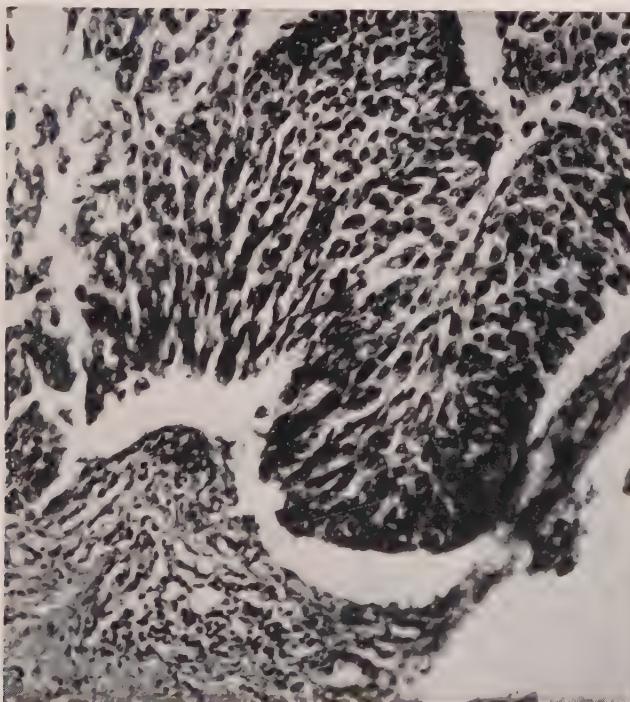


Fig. 491.—Papillary carcinoma of renal pelvis. Microscopic appearance of tumor in Fig. 490.

embryonal types such as a Wilms' tumor. Rare examples of fibrosarcoma and liposarcoma have been reported.

References

General

- Allen, Arthur C.: The Kidney, Medical and Surgical Diseases, New York, 1951, Grune & Stratton.
 Bell, E. T.: Renal Diseases, Philadelphia, 1946, Lea & Febiger.
 Bradley, S. E.: New England J. Med. 229: 364 and 402, 1943; and 235: 755, 1946.
 McManus, J. F. A.: Medical Diseases of the Kidney, Philadelphia, 1950, Lea & Febiger.
 Smith, Homer W.: The Kidney, Structure and Function in Health and Disease, New York, 1951, Oxford University Press.
 Smith, L. W., et al.: Cardiovascular-Renal Disease, New York, 1940, D. Appleton-Century Co.
 Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, 1914, Julius Springer.

Renal Structure and Function

- Hayman, J. M., Jr., Martin, J. W., Jr., and Miller, M.: Arch. Int. Med. 64: 69, 1939 (number of glomeruli).
 Herrin, R. C.: Physiol. Rev. 21: 529, 1941 (renal function tests).
 Jones, David B.: Am. J. Path. 27: 991, 1951.
 Mitchell, N., and Angrist, A.: Arch. Path. 35: 46, 1943 (adrenal inclusions in kidney).
 O'Crowley, C. R., and Martland, H. S.: J. Urol. 50: 756, 1943 (adrenal inclusions in kidney).
 Wilmer, H. A.: Arch. Path. 37: 227, 1944 (renal phosphatase).

Acute Glomerulonephritis

- Baehr, G.: Bull. New York Acad. Med. 14: 53, 1938.
 Bell, E. T.: Am. J. Path. 12: 801, 1936; and 13: 497, 1937.
 Dunn, J. S.: J. Path. & Bact. 51: 169, 1940.
 LaDue, J. S.: Ann. Int. Med. 20: 435, 1944 (edema).
 More, R. H., and Waugh, D.: J. Exper. Med. 89: 541, 1949.
 Murphy, F. D., and Rastetter, J. W.: J. A. M. A. 111: 668, 1938.

Subacute Glomerulonephritis

- Bell, E. T.: Am. J. Path. 14: 691, 1938.

Chronic Glomerulonephritis

- Addis, T.: Am. J. M. Sc. 176: 617, 1928.
 Blackman, S. S., Jr., Goodwin, W. E., and Buell, M. V.: Bull. Johns Hopkins Hosp. 69: 397, 1941.
 Christian, H. A.: Am. J. M. Sc. 196: 761, 1938.
 Ellis, A.: Lancet 1: 34 and 72, 1942.
 Horn, H., Klemperer, P., and Steinberg, M. F.: Arch. Int. Med. 70: 260, 1942 (vascular phase).
 Pruitt, R. D.: New England J. Med. 235: 674, 1946.

Uremia

- Bell, E. T., and Knutson, R. C.: J. A. M. A. 134: 441, 1947 (extraarenal azotemia).
 Bradley, S. E.: New England J. Med. 235: 755, 1946 (biochemical abnormalities).
 Fine, J., et al.: Ann. Surg. 124: 857, 1946 (peritoneal lavage).
 Gouley, B. A.: Am. J. M. Sc. 200: 39, 1940 (myocardial degeneration).
 Harrison, T. R., and Mason, M. F.: Medicine 16: 1, 1937.
 Langendorff, R., and Pirani, C. L.: Am. Heart J. 38: 282, 1947 (heart).
 Murhead, E., et al.: Arch. Surg. 54: 374, 1947 (peritoneal lavage).

- Odel, H. M., and Ferris, D. O.: Proc. Staff Meet. Mayo Clinic 22: 305, 1947 (peritoneal lavage).

Focal Glomerulitis

- Gross, P., and Morningstar, W.: Am. J. Path. 19: 333, 1943.

Experimental Glomerulonephritis

- Fouts, P. J., Corcoran, A. C., and Page, I. H.: Am. J. M. Sc. 201: 313, 1941.
 Horn, H.: Arch. Path. 23: 71 and 241, 1937.
 Medlar, E. M., and Blatherwick, N. R.: Am. J. Path. 13: 881, 1937; and Arch. Int. Med. 59: 572, 1937 (dietary nephritis in rats).
 Seegal, B. C., and Loeb, E. N.: J. Exper. Med. 84: 211, 1946.
 Smadel, J. E.: J. Exper. Med. 64: 921, 1936; 65: 541, 1937; and 74: 345, 1941.

Nephrosclerosis

- Loomis, D.: Arch. Path. 22: 435, 1936.

Arteriosclerosis

- Kimmelstiel, P., and Wilson, C.: Am. J. Path. 12: 45, 1936.
 Klemperer, P., and Otani, S.: Arch. Path. 11: 60, 1931.
 Simonds, J. P.: J. A. M. A. 120: 89, 1942.

Hypertension

- Castleman, B., and Smithwick, R. H.: J. A. M. A. 121: 1256, 1943; and New England J. Med. 239: 729, 1948.
 Dock, W.: New England J. Med. 236: 773, 1947 (circulation in kidneys).
 Goldblatt, H.: Am. J. Med. 4: 100, 1948.
 Goormaghtigh, N.: Am. J. Path. 16: 409, 1940 (juxtaglomerular apparatus).
 Koepsell, J. E., Kuzma, J. F., and Murphy, F. D.: Arch. Int. Med. 85: 432, 1950.
 Moritz, A. R., and Oldt, M. R.: Am. J. Path. 13: 679, 1937.
 Oberling, Charles: Am. J. Path. 20: 155, 1944, and Ann. d'Anat. Path. 1: 216, 1924.
 Richardson, G. O.: J. Path. & Bact. 55: 33, 1943.
 Selye, H., and Stone, H.: J. Urol. 56: 399, 1946.
 Volhard, F.: Stanford Med. Bull. 6: 13, 1948.
 White, B. V., Durkee, R. E., and Mirabile, C.: New England J. Med. 228: 277, 1943.

Infarcts of the Kidney

- Abeshouse, B. S.: Urol. & Cutan. Rev. 49: 661, 1945.
 Hoxie, H. J., and Coggin, C. B.: Arch. Int. Med. 65: 587, 1940.
 Kobernick, S. D., et al.: Am. J. Path. 27: 435, 1951.
 Loomis, D., and Jett-Jackson, C. E.: Arch. Path. 33: 735, 1942.

Cortical Necrosis of the Kidney

- Ash, J. E.: Am. J. M. Sc. 185: 71, 1933.
 Duff, G. L., and More, R. H.: Am. J. M. Sc. 201: 428, 1941.
 Dunn, J. S., and Montgomery, G. L.: J. Path. & Bact. 52: 1, 1941.
 Penner, A., and Bernheim, A. I.: Arch. Path. 30: 465, 1940.
 Trueta, J., et al.: Studies of the Renal Circulation, Springfield, 1947, Charles C Thomas.

Renal Lesions in Disseminated Lupus Erythematosus

- Klemperer, P., Pollack, A. D., and Baehr, G.: Arch. Path. 32: 569, 1941.
 Krupp, M. A.: Arch. Int. Med. 71: 54, 1943 (urinary sediment).
 Stickney, J. M., and Keith, N. M.: Arch. Int. Med. 66: 643, 1940.

Diabetic Glomerulosclerosis

- Allen, A. C.: Arch. Path. 32: 33, 1941.
 Kimmelstiel, P., and Wilson, C.: Am. J. Path. 12: 83, 1936.
 Laippy, T. C., Eitzen, O., and Dutra, F. R.: Arch. Int. Med. 74: 354, 1944.
 Siegal, S., and Allen, A. C.: Am. J. M. Sc. 201: 516, 1941.

Orthostatic Albuminuria

- Rytand, D. A.: Arch. Int. Med. 59: 837 and 848, 1937.

Lipoid Nephrosis

- Bell, E. T.: Am. J. Path. 14: 691, 1938; and 5: 587, 1929.
 Blackman, S. S., Jr.: Bull. Johns Hopkins Hosp. 57: 70, 1935.
 Bradley, S. E., and Tyson, C. J.: New England J. Med. 238: 223 and 260, 1948 (nephrotic syndrome).
 Dunn, J. S.: J. Path. & Bact. 39: 1, 1934.
 Farr, L. E., and MacFadyen, D. A.: Am. J. Dis. Child. 59: 782, 1940.
 Leiter, L.: Medicine 10: 135, 1931.
 Murphy, F. D., Warfield, L. M., Grill, J., and Annis, E. R.: Arch. Int. Med. 62: 355, 1938.
 Schwarz, H., Kohn, J. L., and Weiner, S. B.: Am. J. Dis. Child. 65: 355, 1943.

Fatty Degeneration of Kidneys

- Dible, J. H., and Hay, J. D.: J. Path. & Bact. 51: 1, 1940.
 Fuller, R. H.: Arch. Path. 32: 556, 1941.
 Simonds, J. P., and Lange, J. D.: Am. J. Path. 17: 755, 1941 (in glomeruli).

Calcification of Kidneys

- Anderson, W. A. D.: J. Pediat. 14: 375, 1939; and J. Urol. 44: 29, 1940.
 Goldstein, A. C., and Abeshouse, B. S.: Radiology 30: 544, 1938.
 Martz, H.: Arch. Int. Med. 65: 375, 1940.

Renal Amyloidosis

- Altnow, H. O., Van Winkle, C. C.: Maly, H. W., and Williams, L. E.: Arch. Int. Med. 56: 944, 1935.
 Bell, E. T.: Am. J. Path. 9: 185, 1933.

Hyaline Degeneration of Kidneys

- Rather, L. J.: Stanford Med. Bull. 6: 117, 1948.

Chemical Nephrosis

- Anderson, W. A. D.: South. M. J. 34: 257, 1941 (sucrose).
 Edwards, J. G.: Am. J. Path. 18: 1011, 1942 (mercury).
 Smetana, H.: Arch. Int. Med. 63: 760, 1939 (carbon tetrachloride).
 Wilmer, H. A.: Am. J. Physiol. 141: 431, 1944 (sucrose).
 Zingg, W.: Schweiz. Ztschr. allg. Path. 14: 1, 1951 (sucrose).

Acute Diffuse Interstitial Nephritis

- Matthews, W. R.: South. M. J. 35: 1055, 1942.

Pyelonephritis

- Crabtree, E. G.: J. Urol. 44: 125, 1940 (relation to hypertension).
 Lieberthal, F.: Surg., Gynec. & Obst. 69: 159, 1939.
 Putschar, W. G. J.: J. Urol. 43: 793, 1940.
 Shure, N. M.: Arch. Inter. Med. 70: 284, 1942 (relation to hypertension).
 Weiss, S., and Parker, F., Jr.: Medicine 18: 221, 1939.

Necrosis of Renal Papillae

- Davson, J., and Langley, F. A.: J. Path. & Bact. 56: 327, 1944.
 Edmondson, H. A., Martin, H. E., and Evans, N.: Arch. Int. Med. 79: 148, 1947.
 Günther, G. W.: München. med. Wchnschr. 84: 1695, 1937.
 Harrison, J. H., and Bailey, O. T.: J. A. M. A. 118: 15, 1942.
 Robbins, S. L., Mallory, G. K., and Kinney, T. D.: New England J. Med. 235: 885, 1946.

Syphilis of the Kidneys

- Rich, A. R.: Bull. Johns Hopkins Hosp. 50: 357, 1932.

Tuberculosis of the Kidneys

- Lieberthal, F.: Surg., Gynec. & Obst. 67: 26, 1938.

Hyperparathyroid Renal Disease

- Anderson, W. A. D.: Endocrinology 24: 372, 1939; and Arch. Path. 27: 753, 1939.
 Herbert, F. K., Miller, H. G., and Richardson, G. O.: J. Path. & Bact. 53: 161, 1941.

Renal Damage by Vitamin D

- Goormaghtigh, N., and Handovsky, H.: Arch. Path. 26: 1144, 1938.
 Mulligan, R. M.: Am. J. Path. 22: 1293, 1946.

Renal Calculi

- Anderson, W. A. D.: J. Urol. 44: 29, 1940.
 Flocks, R. H.: J. Urol. 43: 214, 1940.
 Prien, E. L., and Frondel, C.: J. Urol. 57: 949, 1947 (composition).
 Randall, A.: Ann. Surg. 105: 1009, 1937; and Surg., Gynec. & Obst. 71: 209, 1940.
 Winer, J. H., and Mattice, M. R.: J. Lab. & Clin. Med. 28: 898, 1943.

Renal Changes in Gout

- Schnitker, M. A., and Richter, A. B.: Am. J. M. Sc. 192: 241, 1936

Cystine Disease

- Hottinger: Ann. paediat. 156: 257, 1941.
 Roulet, F.: Ann. paediat. 156: 284, 1941.

Sulfonamide Nephrosis

- Abeshouse, B. S., and Tankin, L. H.: J. Urol. 56: 658, 1946.
 Antopol, W., et al.: Arch. Path. 31: 592, 1941.
 Murphy, F. D., Kuzma, J. F., Polley, T. A., and Grill, J.: Arch. Int. Med. 73: 433, 1944.
 Sabin, S. S., et al.: Am. J. Path. 19: 211, 1943.

Hemoglobinuric Nephrosis and Crush Syndrome

- Anderson, W. A. D.: Urol. & Cutan. Rev. 47: 139, 1943.
 Bywaters, E. G. L., and Dible, J. H.: J. Path. & Bact. 54: 111, 1942; and 55: 7, 1943.
 Corcoran, A. C., and Page, I. H.: J. A. M. A. 134: 436, 1947; and Texas Rep. Biol. & Med. 3: 528, 1945.
 Goodpastor, W. E., et al.: Surg., Gynec. & Obst. 82: 652, 1946 (burns).
 Lalich, J. J.: J. Exper. Med. 87: 157, 1948.
 Lucké, B.: Mil. Surgeon 99: 371, 1946.
 Mallory, T. B.: Am. J. Clin. Path. 17: 427, 1947.
 Moloney, W. C., et al.: J. A. M. A. 131: 1419, 1946 (ischemic muscle necrosis).
 Moon, V. H.: J. A. M. A. 134: 425, 1947 (shock).
 Ross, J. F.: New England J. Med. 233: 691, 732, and 766, 1945.
 Trueta, J., et al.: Lancet 2: 237, 1946. Idem: Studies of the Renal Circulation, Springfield, Ill., 1947, Charles C Thomas.

Renal Lesions With Multiple Myeloma

- Foord, A. G.: Ann. Int. Med. **8**: 1071, 1935.
 Forbus, W. D., et al.: Bull. Johns Hopkins Hosp. **57**: 47, 1935.

Renal Lesions in Toxemia of Pregnancy

- Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, 1941, Little, Brown & Co.

Hydronephrosis

- Hinman, F., and Lee-Brown, R. K.: J. A. M. A. **82**: 607, 1924 (pyelovenous reflux).
 Robertson, H. E.: Hydronephrosis and Pyelitis of Pregnancy, Philadelphia, 1944, W. B. Saunders Co.

Congenital Malformations of the Kidney

- Eaton, E. F.: Surg., Gynec. & Obst. **79**: 175, 1944 (renal agenesis).
 Potter, E. L.: J. Pediat. **39**: 68, 1946 (renal agenesis).
 Quinn, W. P.: J. Urol. **44**: 10, 1940 (renal ectopia).
 Wilmer, H. A.: J. Urol. **40**: 551, 1938 (fused kidneys).

Lymphatic Cysts of the Renal Pelvis

- Henthorne, J. C.: Am. J. Clin. Path. **8**: 28, 1938.
 Scholl, A. J.: J. A. M. A. **136**: 4, 1948.

Polycystic Disease of the Kidneys

- Bell, E. T.: Am. J. Path. **11**: 373, 1935.
 Kampmeier, O. F.: Surg., Gynec. & Obst. **36**: 208, 1923.
 Lambert, P. P.: Arch. Path. **44**: 34, 1947.
 McKenna, C. M., and Kampmeier, O. F.: Tr. Am. A. Genito-Urin. Surgeons **26**: 377, 1933.
 Oppenheimer, G. D.: Ann. Surg. **100**: 1136, 1934.
 Roos, A.: Am. J. Dis. Child. **61**: 116, 1941.

Renal Tumors

- Ash, J. E.: J. Urol. **44**: 135, 1940.
 Bowen, J. A., and Bennet, G. A.: J. Urol. **24**: 495, 1930 (pelvic tumors).
 Foot, N. C., and Humphreys, G. A.: Surgery **23**: 369, 1948 (prognosis).
 Frang, C.: J. Urol. **45**: 290, 1941 (lipoma).
 Gordon, M. P., Kimmelstiel, P., and Cabell, C. L.: J. Urol. **42**: 507, 1939 (leiomyoma).
 Harvey, N. A.: J. Urol. **57**: 669, 1947 (carcinoma).
 Higgins, C. C.: Arch. Surg. **38**: 224, 1939 (pelvic tumors).
 Judd, E. S., and Donald, J. M.: Ann. Surg. **96**: 1028, 1932 (sarcoma).
 Kretschmer, H. L.: J. Urol. **39**: 250, 1938 (Wilms' tumor).
 Ladd, W. E., and White, R. R.: J. A. M. A. **117**: 1858, 1941 (Wilms' tumor).
 Masson, P.: Am. J. Cancer **33**: 1, 1938 (Wilms' tumor).
 McCartney, J. S., and Wynne, H. M. N.: Am. J. Cancer **26**: 151, 1936 (liposarcoma).
 Melicow, M. M.: J. Urol. **51**: 333, 1944 (classification).
 Moolten, S. E.: Arch. Int. Med. **69**: 589, 1942 (in tuberous sclerosis).
 Owen, C. I.: Am. J. Clin. Path. **8**: 302, 1938 (glomeruloma).
 Patch, F. S.: New England J. Med. **200**: 423, 1929 (pelvic tumors).
 Pemberton, J. de J., and McCaughan, J. M.: Surg., Gynec. & Obst. **56**: 110, 1933 (lipoma).
 Priestley, J. B.: J. Urol. **40**: 269, 1938 (fatty replacement of renal parenchyma).
 Roth, L. J., and Davidson, H. B.: J. A. M. A. **111**: 233, 1938 (fatty replacement of renal parenchyma).
 Robertson, T. D., and Hand, J. R.: J. Urol. **46**: 458, 1941 (lipoma).
 Schiller, W.: Arch. Path. **33**: 879, 1942 (carcinoma).
 Swan, R. H. J., and Balme, H.: Brit. J. Surg. **23**: 232, 1935 (hemangioma).
 Thomas, G. J., and Regnier, E. A.: J. Urol. **11**: 205, 1924 (pelvic tumors).
 Trinkle, A. J.: Am. J. Cancer **27**: 676, 1936 (adenoma).
 Wood, D. A.: J. Urol. **51**: 235, 1944 (Wilms' tumor in adult).

Chapter 22

THE LOWER URINARY TRACT AND MALE GENITALIA

S. B. PESSIN

URETER

Anomalies

Although ureteral anomalies are quite common, necropsy statistics substantiate the fact that many individuals having anomalies of ureters never experienced ill effects. Nevertheless, the anomalies of the ureters are of great importance because of their susceptibility to complications. The various types of anomalies are duplication, malposition, abnormalities of the lumen, and abnormal termination.

Variation of number of ureters is the most common anomaly and the incidence is about 1 to 4 per cent. The bifid or Y-shaped ureter associated with double kidney pelves is the most frequent anomaly. The ureters usually unite at various levels before reaching the bladder. The caudal bifid or inverted-Y ureter, in which a single ureter arising from the pelvis bifurcates distally and terminates with two orifices, is rare. Blind-ending bifurcations mistaken for diverticula are also rare. Other rare anomalies are complete duplication and triplication.

Displaced ureters are caused by aberrant blood vessels and are most frequently associated with malformed and solitary kidneys. Postcaval ureters, 35 of which have been reported in the literature, is associated with faulty development of the inferior vena cava.

Anomalies of the lumen of the ureter consist of strictures, kinks, twists, diverticula, and dilatation. Congenital strictures are usually encountered in the fetus and newborn. They frequently occur at the locations of normal anatomic narrowing. Kinks and twists are associated with aberrant blood vessels, megaloureters, and hydro-ureters. Diverticula are rare. Congenital dilatation or megaloureter is usually bilateral and thought to be of neurogenic etiology. Hypoplasia of ureter is invariably associated with renal agenesis.

Abnormal termination (ectopic openings) in the male is encountered in the prostatic urethra, ejaculatory duct, seminal vesicles, and vas deferens. In the female, ectopic openings occur in the urethra, vagina, uterus, and fallopian tubes. The ureter may also terminate in the rectum and various places in the urinary bladder other than the normal location.

Inflammation

Ureteritis.—Nonspecific inflammation of the ureter is usually secondary to pyelonephritis, cystitis, and retroperitoneal infections. Pri-

mary nonspecific ureteritis is not uncommon and has been associated with tonsillectomy, pharyngitis, sinusitis, colitis, and prostatitis.

Ureteritis Cystica.—The incidence of ureteritis cystica is probably greater than the seven cases which the writer found in 1,590 consecutive necropsies. The disease has been diagnosed roentgenologically and the cysts have been ruptured by ureteral catheterization to relieve obstruction. Ureteritis cystica may occur at any age but it is far more prevalent in people past the sixth decade. The cysts are formed by central degeneration of the so-called cell nests of von Brunn, which probably develop from focal downgrowth of mucous membrane as a consequence of ureteritis. They occur more frequently in the upper third of the ureter and are usually most numerous at the ureteropelvic junction. They range in size from microscopic proportions to 2 cm. in diameter. Occasionally they are pedunculated. A cluster of cysts or a single cyst may cause obstruction of the ureter. A single cyst caused obstruction in one of the author's cases. Their contents may be watery or viscid or contain a colloidlike material. They may be colorless, straw-colored, yellowish-brown, bluish, or dark red. The microscopic cysts are lined with one to several layers of cuboidal epithelial cells. The macroscopic cysts may be lined with a single layer of flat, cuboidal, or columnar cells. This cystic condition may be unilateral or bilateral and is not infrequently associated with pyelitis cystica and cystitis cystica. The pathogenesis of this disease is included in the subject of cystitis.

Follicular Ureteritis (Ureteritis Granulosa).—Follicular ureteritis is rather rare. It is characterized by multiple elevated, flat or rounded, pinkish or red areas which microscopically reveal collections of lymphocytes sometimes in typical follicle formation. Obstruction or hemorrhage is not an uncommon complication.

Specific Ureteritis.—Although tuberculosis of the ureter is commonly associated with renal tuberculosis of considerable duration, authentic cases of primary tuberculosis of ureters appear in the literature. It is a hematogenous infection usually associated with pulmonary tuberculosis. In some cases of extensive tuberculosis of the kidney and bladder, the ureter is entirely unaffected. *Syphilis* of the ureter is extremely rare and its involvement is due to extension from the bladder or kidney. *Gonococcal ureteritis* is secondary to gonococcal cystitis. Cases of *actinomycosis* infection, *bilharzial infestation* and *hydatid* disease involving the ureter may be found in literature.

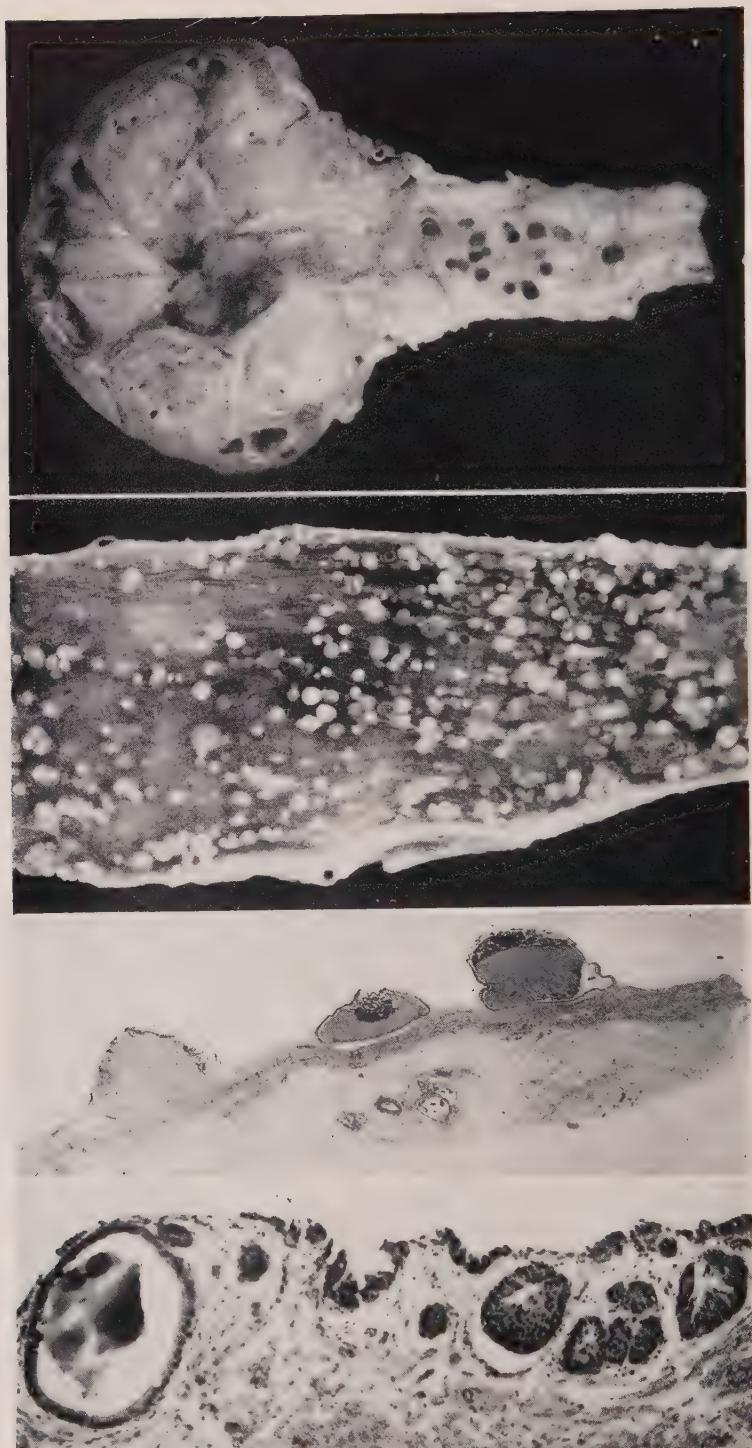


Fig. 492.—Ureter: *A*, Ureteritis cystica and pyelonephritis; *B*, ureteritis cystica from a case associated with cystitis and pyelitis cystica; *C*, cysts lined with single rows of columnar epithelial cells; *D*, cell nests of von Brunn.

Obstruction

Stricture.—Ureteral stricture may be congenital or acquired. About two-thirds of congenital strictures are located at the ureteropelvic junction and the majority of the remaining third at, or in, the bladder wall. In true congenital stricture there is either thickening of the ureteral wall due to hypertrophy of the muscularis and hyperplasia of the fibrous tissue or merely a narrowing of the ureter at the point of obstruction. Acquired strictures may be due to a variety of inflammations, tumors, operations, and healed erosions produced by calculi or trauma. Obstruction at the ureteropelvic junction is due to true stenosis, extra ureteral pressure by anomalous blood vessels, horizontal axial rotation of the kidney, and nephrophtosis which causes kinking of the ureter.

Kinks and Angulations.—Kinks and sharp angulations occur in any part of the ureter but are more common at the ureteropelvic junction. They are more common in females and involve the right ureter more frequently than the left. They may be congenital or acquired. They are due to abnormal length of ureter, lack of proper rotation of the kidney, pressure by anomalous blood vessels, adhesions, tumors, and retroperitoneal inflammation. Kinks are frequently associated with ptosis of the kidney.

Dilatation

Hydro-ureter and Megalo-ureter.—Dilatation, tortuosity, and elongation of the ureter may be obstructive or nonobstructive, either of which may be congenital or acquired. The nonobstructive type is due to loss of muscle tone as a result of disturbed innervation (megaloureter) or inflammation. The term megaloureter should be reserved for enormous congenital dilatation of the ureter with atonic ureteral orifice, dilated renal pelvis, and no evidence of infravesicle obstruction. Some of the causes of obstructive type of hydro-ureter have been previously mentioned under the subject of stricture. Other conditions causing hydro-ureter are intraluminal obstructions by calculi, tumors, and organized blood clots. If the obstruction is in the ureter, it will become dilated and distorted, and hydronephrosis will develop on the affected side. If, however, obstruction is below the ureteral orifices, both ureters will be dilated and there will be bilateral hydronephrosis. The "hydro-

ureter of pregnancy" is perhaps due to loss of ureteral tonicity or to endocrine effect (endocrine activity of placenta).



Fig. 493.—Ureter, large papillary carcinoma involving upper third of the ureter.

Ureterocele.—Ureterocele is an intravesical dilatation of the ureter. It must be differentiated from prolapse of the ureter. In prolapse, the intravesical protrusion is covered by ureteral mucosa, whereas the ureterocele is covered by bladder mucosa. Ureterocele is either congenital or acquired, occurs at all ages, and is more common in women. It involves the left ureter more often than the right. Ureteroceles may be round or elongated, open or closed. They vary considerably in size; some almost fill the entire bladder. The ureteral orifice is usually located at the apex of the ureterocele. The intravesical portion of the cyst wall consists of three layers: (1) bladder mucosa (intravesical surface), (2) connective tissue, (3) ureteral mucosa. In females the ureterocele may prolapse through the urethra.

Prolapse.—Prolapse of the ureter is a rare condition in which the ureter protrudes into the bladder. It is usually associated with the passage of renal calculi and is probably de-

pendent on structural weakness of the wall and redundancy of the ureter.

Diverticula.—Ureteral diverticula are rare. They may be congenital or acquired, true or false. All true diverticula are congenital. They are ovoid or round, contain all coats of ureter and communicate with the ureteral lumen through a distinct stoma. They may contain a few cubic centimeters of urine or up to as much as 3,500 c.c. They may occur at any portion of ureter but are usually located in the lower third closer to the ureteral orifice. Due to stagnation of urine, calculi frequently develop in them. False diverticula (probably a misnomer) are protrusions of mucosa through the muscular wall.

Calculi

Most calculi encountered in the ureter are of renal origin. The possibility of development of calculi above a ureteral stricture or in a diverticulum cannot be discounted. Most calculi are composed of calcium oxalate, calcium phosphate, and uric acid. The tendency of the calculus to remain in its pure form depends on the sterility of the urine. If infection is present, phosphatic deposits develop. Calcium oxalate calculi predominate. Involvement of both ureters is rare. About 80 per cent of ureteral calculi occur in males between the ages of 20 and 50 years. The calculi may become impacted in any part of the ureter. The most common locations of the arrest of the calculus are at (1) ureteropelvic junction, (2) location where ureter crosses iliac vessels, (3) base of broad ligament in females and vas deferens in males, (4) entrance of ureter at external muscle layer of bladder, (5) ureteral orifice. Impacted calculi may cause a variety of complications such as hemorrhage in early stage of impaction, ureteritis, hydronephrosis, pyelonephritis, diverticulum formation, periureteritis, or periureteral abscess. Multiple calculi are present in about 10 per cent of the cases. Most of the calculi are small. Several unusually large calculi have been reported. In Goldman's⁷ case, the calculus measured 18 cm. in length and weighed 132 grams.

Tumors

Leukoplakia.—Although listed as a precancerous lesion, it is doubtful whether leukoplakia has ever developed into a malignant neoplasm in the ureter. It is seldom seen in a surgical specimen. The writer saw leukoplakia of the kidney pelvis extending down the ureter in a surgical specimen having multiple calculi. Most of the cases have been found at necropsy.

Benign Tumors.—Fibromas, myomas, fibromyomas, and angiomas are among the rare tumors that may involve the ureter. Some of these tumors may be attached by a pedicle.

Malignant Tumors.—The most common tumor, but not always malignant, is the transitional cell papilloma. The behavior of this tumor is similar to the simple papilloma of the urinary bladder. Transitional cell carcinomas of the ureter may be papillomatous or flat and ulcerating and comprise about 1 per cent of all car-

cinomas of the upper urinary tract. The etiology, morphology, and, to a certain degree, the behavior of ureteral carcinomas are similar to those of the bladder. No age is exempt, but most occur between the ages of 45 and 65. The youngest patient on record was 22 years of age and the oldest 89 years. In about 75 per cent of the cases the tumor is found in the lower third of the ureter. The tumor may protrude into the bladder through the ureteral orifice. Histologically, the most common tumor is the papillary transitional cell carcinoma. Squamous cell carcinomas and adenocarcinomas are rare. Metastasis occurs earlier and is more extensive than the bladder tumors. Metastasis may be encountered in lymph nodes, liver, vertebrae, lung, kidney, spleen, brain, pancreas, prostate, pericardium, and skin.

The ureter is more likely to be involved by secondary tumors than by the primary. The most common tumors to metastasize to the ureter originate from kidney, bladder, testicle, stomach, and retroperitoneal tumors.

URINARY BLADDER

Anomalies

Arrested or abnormal embryological development may give rise to a great variety of congenital anomalies. Absence, duplication, and hourglass formation of the bladder are very rare. Failure or imperfect development of the urachus causes urinary fistulas, sinuses, cysts, and diverticula of the bladder. Failure of development of the urorectal septum (division structure of cloaca) may cause a vesicovaginal and vesicorectal fistula.

Extrophy.—The most important anomaly is extrophy of the urinary bladder. It occurs about once in 30,000 births and is about seven times more frequent in the male. In this anomaly, the anterior wall of the bladder and the overlying lower anterior abdominal are absent so that the inner surface of the posterior wall is everted and protrudes in the region of the lower anterior wall of the abdomen. Several theories of this anomaly have been proposed. The most likely theory is the failure of union of the urogenital cleft. In typical complete extrophy, there is absence of the symphysis pubis. A variety of other congenital malformations may be present with this condition, such as absence or malformation of the following structures: penis, scrotum, prostate, labia, clitoris, vagina, and uterus. Spina bifida and prolapse or atresia of the rectum may be accompanying anomalies. About 50 per cent of the patients die before the age of 10 due to development of hydronephrosis or pyelonephritis. About 70 per cent die before the age of 20. A few patients have survived well into adult life.

Hemorrhage

Both hyperemia and hemorrhage of the bladder may be due to inflammation, tumors, calculi, blood dyscrasias, parasites, foreign bodies, and trauma.

Inflammation (Cystitis)

Pathogenesis.—Inflammation of the urinary bladder is the most common secondary infection, but as a primary disease it is rather unusual. The normal urinary bladder is very resistant to infection. The most important factors in preventing infection are the external and internal sphincters serving as barriers, the frequent washing of the mucosa each time the bladder completely empties, the smooth pavement epithelium, and the lack of glands.

The urethra, especially the short female urethra, is the most common route of infection (ascending infection). Descending infection from the kidney ranks second. Occasionally, the infections may be hematogenous and in rare instances lymphogenous. The direct agents causing cystitis are: (1) bacteria, (2) chemical irritants, (3) mechanical irritants, (4) parasites, and (5) fungi. The various bacteria that may incite inflammation are *Escherichia coli*, *staphylococcus*, *streptococcus*, *Bacterium aerogenes*, *Neisseria catarrhalis* and *gonorrhoeae*, *pneumococcus*, various diphtheroids, and in very rare instances *Mycobacterium tuberculosis* and *Treponema pallidum*. Fungus and parasitic infections are rare, and the usual ones encountered in the literature are due to actinomycetes, monilia, and trichomonas. Schistosomiasis is quite common in certain tropical regions. Various chemical agents, especially those containing heavy metals such as lead, arsenic, and mercury, are very irritating to the bladder mucosa. Calculi and various foreign bodies (retention catheters) are common mechanical irritants. The most common predisposing causes of cystitis are obstruction of outflow of urine, vesical paralysis, and lowered resistance in chronic debilitating diseases. Cystitis may be acute or chronic, focal or diffuse. The most frequent site of focal inflammation is in the trigone (trigonitis).

Acute Cystitis.—Acute cystitis or acute exacerbation of chronic cystitis may be catarrhal, fibrinopurulent, purulent, diphtheritic, ulcerative, hemorrhagic, or gangrenous. Any of these forms may be in combination. In mild inflammation the mucosa is hyperemic, edematous, and infiltrated with lymphocytes and a few polymorphonuclear neutrophiles. The swollen epithelial cells have a tendency to desquamate. In moderate and severe forms of acute cystitis, the gross picture varies considerably. At first, there is a marked hyperemia of the mucosa and submucosa. This is followed by multiple hemorrhages in the submucosa and superficial ulceration of the mucosa may develop. As the inflammation progresses,

the bladder wall becomes more thickened and infiltrated with neutrophilic leukocytes so that at times there is a diffuse purulent cystitis or there may be small intramural abscesses. The ulcers become coated with fibrin, bacteria, and various precipitates of urine. The color of the ulcer, pseudomembrane, or crust depends on the changes of the blood, character of the bacteria, and the amount and type of deposited urine sediment. The urea-splitting bacteria cause the urine to become very alkaline so that the ordinary dissolved minerals precipitate out. When necrosis supervenes, the picture is that of a hemorrhagic gangrenous cystitis. In very pronounced cases, the surface becomes shaggy due to adherent fibrin, mucopurulent exudate, and projecting necrotic tissue.

Chronic Cystitis.—In chronic cystitis, one or all of the layers of the bladder may reveal chronic inflammation. Quite frequently, it is an interstitial inflammation and may be accompanied by pericystitis. It may follow one or repeated attacks of acute cystitis. In chronic interstitial cystitis the capacity of the bladder is decreased due to fibrosis, thickening of the wall, and decreased elasticity. The mucosa is rather dull, frequently roughened, and contains focal areas of dilated blood vessels. The gross and microscopic changes of chronic cystitis with its acute exacerbations vary markedly and depend on (1) individual variability of tissue reaction, (2) intensity of the infection, and (3) the causative agent.

SPECIAL FORMS OF CYSTITIS

Gangrenous Cystitis.—Gangrenous cystitis occurs in severe infections, trauma, extravesical pressure (pregnancy, tumors, etc.), x-ray and radium reactions, circulatory obstruction of adjacent arteries, and injection of chemicals. Occasionally it follows transurethral prostatic resection. This serious infection occurs more frequently in women. Either the mucosa alone or all of the layers of the bladder may be involved. The mucous surface appears rough, shaggy, dirty, grayish with purplish and black areas. The mucosa may be cast off in fragments or en masse.

Encrusted Cystitis.—Alkaline encrusted cystitis may become a stubborn chronic infection. The majority of cases occur in women after parturition. The inflamed bladder is invaded by urea-splitting bacteria, causing production of ammonia, and, consequently, the precipitation of urinary salts. The crystals

settle on any injured portion of the bladder, forming whitish, grayish-white granular, flat or slightly elevated patches (crusts).

Cystitis Cystica.—A not infrequent finding at postmortem examination is the presence of single or multiple cysts projecting from the mucosa. Usually there is an associated chronic cystitis. The writer has seen one case of multiple cysts of the bladder without microscopic evidence of inflammation. Although the inflammatory basis as an exciting factor of the development of these cysts is doubted by some observers, the fact remains that by far the great majority of cystic bladders are associated with cystitis. Cysts have been found in various infections, strictures of the neck of the bladder and urethra, prostatic obstruction, cystolithiasis, bilharzial infestation, and carcinoma of the bladder. The histogenesis of these cysts was clearly described by von Brunn. Microscopic studies of bladders harboring these cysts reveal epithelial sprouts arising from the mucosa and extending down into the submucous fibrous tissue. One part, usually the uppermost, of the epithelial downgrowths thins out to form a connecting epithelial stalk. The stalk eventually becomes severed (probably pinched off by proliferating fibrous tissue) from the overlying mucosa. The resulting epithelial bodies, lying in the submucous fibrous tissue known as epithelial nests ("epithelnesten") of von Brunn, may proliferate, undergo central degeneration with liquefaction and formation of microscopic cysts which gradually become larger. Some sprouts become cystic without being detached from the mucosa. Some cysts remain microscopic in dimension whereas others enlarge, push upward, and project above the surface. The macroscopic cysts range in size from less than 1 mm. to 3 cm. in diameter. The majority are spherical, but some are ovoid and occasionally attached by a pedicle. The color of the cysts varies from colorless, to gray, various shades of amber, orange, red, brown, or bluish. The contents may be watery or thick and viscid. The cysts may be lined with one to several layers of epithelial cells. The single-layered cysts are lined with either flat, cuboidal, or columnar cells. The columnar cells often secrete mucus since the content of such cysts is mucoid in character. It is believed that such cysts originate from enteric gland rests or from transitional epithelial cells which differentiate into secretory type of cells. Some authors believe that cystitis glandularis originates from cell nests of von Brunn. This idea is not held by the writer. Some investigators believe that cystitis cystica and cystitis glandularis are pre-cancerous lesions and may lead to development of adenocarcinoma.

Malakoplakia.—The etiology of malakoplakia is not known. This uncommon granulomatous inflammation occurs predominantly in women past 30 years of age who have had frequent bouts of cystitis. Malakoplakic lesions have been found in children. The lesions are multiple, discrete, or confluent, soft, grayish-yellow or yellowish-brown, well-defined, slightly raised plaques or nodules, frequently having depressed centers and often surrounded by a zone of hyperemia. They vary in size from 1 mm. to more than 5 cm. in diameter. Micro-

scopically, the lesions are granulomatous in character. In addition to the usual inflammatory cellular elements there are many large and medium-sized, rounded and polyhedral cells having abundant granular and vacuolated cytoplasm and well-defined cell membranes. The mononuclear cells frequently phagocytose bacteria, erythrocytes, and cellular debris. The most characteristic feature of malakoplakia is the presence of calcospherites which, if uniform in size and not laminated, have the appearance of yeastlike fungi. The first lesion seen by the writer was thought to be a monilia infection until cultures of urine and tissue yielded negative results. These peculiar spherules are known as Michaelis-Gutmann bodies. They are commonly phagocytosed by macrophages and giant cells. They range in size from 1 to 10 microns in diameter. The small bodies are round or oval, homogeneous, and frequently refractile. The larger forms may have fine crenations and may be concentrically laminated. They have a strong affinity for hematoxylin. They reveal high calcium content with von Kossa stain. Hemosiderin may be demonstrated in them with Gomori iron reaction. Malakoplakia, in rare instances, may extend to involve the ureters, kidney pelvis, and the kidney parenchyma.

Follicular Cystitis.—Follicular cystitis is characterized by aggregations of numerous tiny grayish or yellowish elevated nodules some of which are surrounded by a reddish zone. Microscopically, there are numerous discrete collections of lymphocytes in the submucosa. Well-defined follicles of larger lymphocytes with pale nuclei are in the centers of the collections. The trigone is the most frequent seat of this rare disease.

Glandular Cystitis.—Another rare disease, principally involving the trigone and frequently occurring in extrophied bladders, is cystitis glandularis. It is characterized by the presence of simple glands or glandlike spaces lined with cuboidal or columnar epithelial cells. These glandular structures may be open on the mucosal surface. The condition is associated with varying degrees of inflammation. Two types of glands are recorded: glands of Albaran which probably originate from cell nests of von Brunn (see cystitis cystica), and enteric type of glands. It is the writer's opinion that true cystitis glandularis contains mucus-secreting enteric glands.

Emphysematous Cystitis.—Emphysematous cystitis is a rather rare condition in which the mucosa is studded with gas-filled vesicles. It occurs most frequently in diabetic patients, and may be due to either bacterial fermentation of glucose present in the mucosa and submucosa, or enzymic action of these tissues when bacteria are absent. In the nondiabetic cases, the formation of vesicles is due to gas-forming bacilli of the Clostridium group. Air or gas-producing bacteria may gain entrance by instrumentation or catheters. Grossly, the mucosa may show various gradations of hyperemia with prominent silvery bubbles ranging in size from 1 to 10 mm. in diameter. Microscopically, most of the

vesicles are situated beneath the mucosa and their walls are composed of compressed fibrous tissue.

Bullous Cystitis.—Pronounced edema of the mucosa and submucosa is manifested as large bullae which at times may simulate polypi. It occurs in a variety of inflammatory conditions, but it is most commonly seen in uremia and early irradiation cystitis. It may be localized

a Hunner's ulcer because frequently no definite ulcer is seen. Therefore, it would seem that the term, interstitial cystitis, is most appropriate. The lesion occurs almost exclusively in women. The youngest reported was 17 and the oldest 84. The highest incidence is in middle-aged women. The etiology is not known. It is often associated with endocervicitis, lymphatic obstruction, and bladder spasm in women under

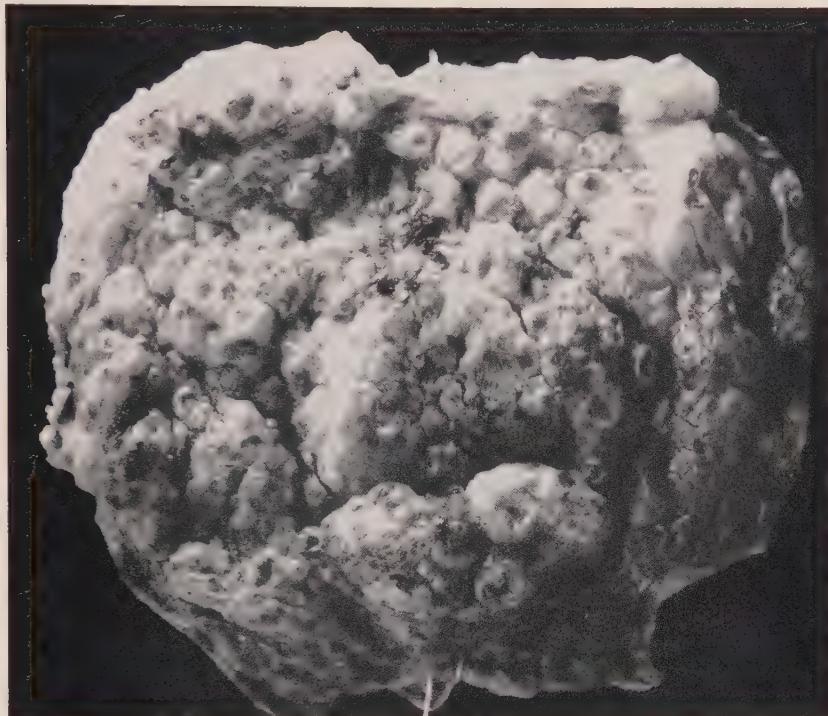


Fig. 494.—Cystitis emphysematosa.



Fig. 495.—Section through bladder wall showing multiple submucous gas-filled vesicles.

or may involve the entire bladder. The bladder wall is thick and edematous, and the mucosa is thrown into folds and polypoid masses. The edema may involve all of the layers or may only affect the submucosal connective tissue. Inflammatory cellular reaction is usually scanty.

Interstitial Cystitis (Hunner's Ulcer; Localized Submucous Fibrosis).—There is no unanimity of opinion regarding what constitutes

nervous tension. Some maintain that the lesion begins as a lymphedema, initiated by a certain strain of streptococcus, that ultimately causes marked fibrosis. Its similarity to lupus erythematosus has been emphasized. Others have pointed out that it may be an embolic process. The lesion (single or multiple) usually begins in the dome or anterior wall of the bladder. Grossly, the involved area appears

thick, has an uneven usually smooth surface with a faint ulcerated or excoriated area. When there is considerable submucosal fibrosis the surface has a stellate pattern with bands radiating in all directions, and where these bands converge there may be small tears or excoriations. Microscopically, the surface epithelium is flattened, thin, and denuded in the ulcer-bearing area. In the early stages the submucous connective tissue is edematous and infiltrated with lymphocytes and the excoriated area is coated with fibrin. Later, an increased amount of fibrous tissue develops in the submucosa and the intermuscular stroma becomes edematous and likewise increased. As the lesion spreads, there is increased fibrosis, with cicatricial contraction so that the capacity of the bladder becomes diminished. In advanced fibrosis, the bladder may shrink to a capacity of only 2 or 3 ounces of urine.

Abacterial Exudative Cystitis.—This disease is usually associated with Reiter's disease in which there may be bilateral conjunctivitis and polyarticular arthritis. The urine contains many polymorphonuclear neutrophiles and no bacteria. Bacterial cultures of urine have been repeatedly negative. The mucosa is edematous, somewhat hyperemic, and may contain superficial ulcers.

Tuberculosis.—Although tuberculosis of the bladder may be secondary to tuberculosis of the prostate, seminal vesicles, or associated with generalized miliary tuberculosis, the majority of cases of tuberculous cystitis are due to implantation of tubercle bacilli from the upper urinary tract. Early lesions appear as miliary tubercles around the orifices of the ureters. The tubercles break down to form minute ulcers which coalesce, forming large irregular ulcers. Widespread ulceration with concomitant

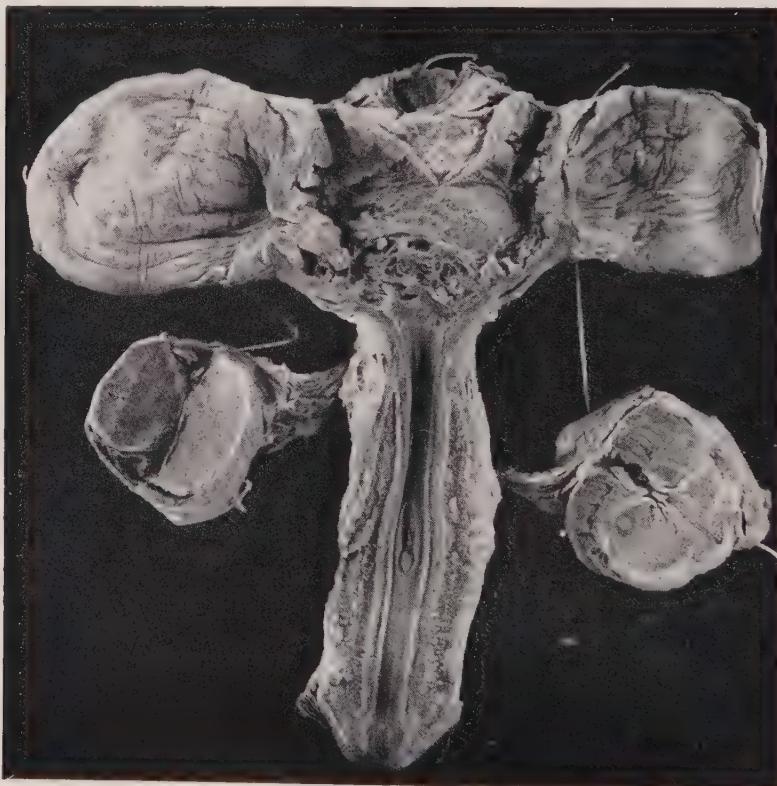


Fig. 496.—Tuberculous ulcers of the urinary bladder and ureter; caseous tuberculosis of the epididymides and left testicle.

Phlegmonous Cystitis.—This is a rare finding and is comparable to phlegmonous gastritis. The purulent exudate may be localized, circumscribed, and become an intramural abscess, or the entire wall may be diffusely infiltrated with polymorphonuclear leukocytes. It may be initiated by damage to the mucosa as a result of various forms of trauma, or it may be found associated with ulcers or neoplasms.

fibrosis causes contraction of the bladder. When the entire wall is infiltrated with tuberculous granulation tissue, there is associated pericystitis with adhesions.

Syphilis.—The rare lesions of secondary syphilis involving the bladder consist of macules, papules, or whitish mucous patches similar to those occurring in the oral mucosa. Gummas of tertiary syphilis are more common. They

occur more frequently in the trigone, especially around the ureteral orifices. They are single or multiple grayish-yellow ulcerations with elevated margins.

Mycotic Infections.—The rather rare *actinomycotic* infection of the urinary bladder is usually secondary to invasion of actinomycetes from adjacent visceral involvement or implantation from renal actinomycosis. Grossly, the lesions may resemble tuberculosis, and, microscopically, actinomycetes may be demonstrated in the granulation tissue. *Monilia* cystitis has been reported with generalized moniliasis; however, in females monilia may invade the bladder by way of the urethra in cases of monilia vaginitis. Grossly, the mucosa contains soft, pearl-white, slightly elevated patches. These patches are quite firmly adherent to the mucosa which bleeds when they are removed. Many yeast-like spores and occasional filaments are present in the scrapings from the patches. Other yeasts and molds may become secondary parasitic invaders and produce lesions in the bladder.

Parasitic Infections.—*Schistosoma haematum* (schistosomiasis, bilharziasis) infestations cause a variety of unusual lesions in the bladder (see discussion, page 383). Trichomonas cystitis is not infrequent in the female but rather rare in the male. The writer has seen two cases in males whose urine contained many trichomonads. The mucosa is thickened, somewhat granular, and may contain pearly-white patches with sharply demarcated borders around which there are punctate hemorrhages. Infestations of the bladder with *Echinococcus* and *Strongyloides stercoralis* have been reported.

Grain Mite Infestation.—A peculiar inflammation of the trigone of the bladder has been infrequently reported as being due to a grain mite that lives on wheat, straw, cheese, flour, bread, and other foodstuffs. The parasites are sporozoa belonging to *Tyroglyphus* and *Tars-nemidae* families. The diagnosis is made by finding the grain mite in the urine. The mode of entrance into the bladder is not definitely known. Three ideas prevail: (1) direct entrance into urethra from contaminated hands or clothing, (2) common infection of intestine and mite gains entrance from anus to urethra, and (3) eggs of mites proceed through intestinal tract into kidney and hatch in the bladder.

Irradiation Cystitis.—Irradiation cystitis produced either by roentgen ray or radium exposure causes characteristic lesions. In the early stage, there may be a bullous cystitis involving the posterior wall. Later, small granulomatous red-colored excrescences appear. These may aggregate in groups. Indolent ulcers with marginal telangiectasis may develop after months or years following irradiation. In one of the author's cases that came to necropsy such ulcers developed seven years after irradiation for carcinoma of the cervix. Mucosal atrophy is not uncommon. Microscopically, there is telangiectasia of the veins and lymphatics, hyaline fibrosis, and thickening of the arteries. The mucosa is usually atrophic or may undergo squamous cell metaplasia. Complications are ureteral strictures and vesicorectal and vesicovaginal fistulas.

Changes in Size and Form

Dilatation of the bladder may be due to stricture of the urethra, obstruction of the vesicle neck, and neurogenic dysfunction often designated as paralysis of the bladder. If obstruction is acute or of short duration as in postoperative pelvic surgery, no permanent gross or histologic changes develop. If obstruction is of long duration, the dilatation may be accompanied by compensatory hypertrophy.

Hypertrophy of the urinary bladder may be concentric or eccentric. Concentric hypertrophy is usually due to irritation as in inflammation, calculi, foreign bodies, etc. The bladder maintains its normal capacity. Eccentric hypertrophy is predominantly due to obstruction to outflow of urine. The thickening of the wall is due to hypertrophy of the interlacing bands of smooth muscle and increase of connective tissue. Externally the bladder appears wrinkled, and internally there is prominent crisscrossing of hypertrophied muscle bundles, often described as trabeculation of the bladder. Between the muscle bundles there are small pockets or cellules.

Diverticula may be single or multiple, congenital or acquired, and true or false types. A true diverticulum is usually a congenital outpouching in which the wall contains all of the layers of the bladder. A false diverticulum is usually acquired and is formed by a herniation of the inner lining through a defect of the outer lining. The starting points involve the cellules formed between thickened trabecular muscles of hypertrophied bladders. Most of these diverticula occur in males with large prostates between the ages of 50 and 70 years. Diverticula range in size from about 1 cm. in diameter to a sac holding more than a liter. Diverticula are multiple in the majority of the cases. Some diverticula are multilocular. It is interesting to note that acquired diverticula occur more frequently at the sites of congenital forms (posterior or lateral wall near ureteral orifices and at the site of urachus) and therefore, pre-existing weakened foci are perhaps a predisposing factor. The neck of a false diverticulum is always narrow. The wall of false diverticula is composed of mucosa, connective tissue, and a few smooth muscle strands. Infection may lead to vesicle diverticulitis, ulceration, and lithiasis.

Herniation of the bladder through the inguinal or femoral rings may occur at any age but is prevalent in later adult life. Congenital or acquired weakenings of the abdominal wall, increased intra-abdominal pressure (gravid uterus, etc.), overdistention of bladder, and trauma are some of the most important factors influencing the development of bladder herniation. This type of herniation is not uncommonly an accidental finding in operations for inguinal and femoral hernias.

Cystocele is a protrusion of the bladder into the vagina due to relaxation of the various pelvic supports and is frequently associated with rectocele and retrodisplacement of the uterus. The bladder pushes against the anterior wall of the vagina producing a soft fluctuating mass.

Prolapse of the bladder is quite rare. It occurs only in the female. Relaxation of supporting ligaments and sphincters, an aftermath of difficult labor with addition of intraabdominal pressure such as straining at stool, may cause the upper part of bladder to invert and herniate through the urethra. Gangrene may rapidly develop because of pressure on the blood vessels.

Stenosis (Marion's disease) involving the bladder neck may be congenital or acquired. In congenital stenosis, a diaphragm composed of muscle and fibrous tissue obstructs the proximal end of the urethra. This diaphragm contains a small opening. The acquired type occurs almost exclusively in males as a result of scarring and narrowing of the bladder neck and prostatic urethra associated with fibrous type of prostate and prostatitis. Microscopically, the congenital diaphragm is composed of normal muscle and fibrous tissue devoid of inflammation whereas the acquired type contains very few muscle fibers, much fibrous tissue and inflammatory cellular infiltration.

Spontaneous Rupture

Trauma and foreign bodies are the most frequent causes of rupture of the bladder. Spontaneous rupture of the bladder is always due to overdistention. The perforation is intraperitoneal. The chief causes are as follows: (1) obstruction due to enlargement of the prostate gland, (2) urethral stricture, (3) alcohol intoxication dulls the sensorium and delays the urge to void, (4) neurogenic dysfunction, (5) postoperative retention, and (6) necrosis of the wall in long-standing severe cystitis and neoplastic infiltration.

Vesical Calculi

Most vesical calculi are of renal origin and associated with pyelonephritis, or are caused by metabolic or endocrine disturbances. Calculi developing in the urinary bladder may be of inflammatory or noninflammatory origin. Among the most common causes are imperfect emptying of bladder due to obstruction or paralysis, infection, foreign bodies, inadequate amount of vitamin A, and faulty metabolism of calcium, uric acid, cystine, or xanthine. The incidence of primary bladder calculi in the United States is relatively low compared to other parts of the world, especially Southern China and India. In the wet tropics bladder stones are extremely rare.

Vesical calculi may be single or multiple. They vary in size from a sand particle to several centimeters. Lepreau and Jenkins⁴⁵ reported a calculus removed from a man aged 34 years, weighing 1,134 grams (2½ pounds).

The production of inflammatory calculi is assisted by urea-splitting bacteria rendering the urine highly ammoniacal. These calculi are composed of ammonium magnesium phosphate, calcium phosphate, ammonium urate, and calcium oxalate. Phosphatic calculi are rounded, slightly granular, and of chalky consistency.

The most important noninflammatory vesical calculus is of urate composition, chiefly ammonium urate mixed with sodium urate and

uric acid. It is small, firm, and yellowish-brown. Other noninflammatory calculi, mainly of renal origin, are oxalate (light or dark brown), cystine (white or pale yellow), and xanthine (smooth and brownish-red). Noninflammatory calculi may be heavily coated with a lamellated layer of ammoniacal salts in the presence of cystitis. Complications of vesical stones are obstruction, bladder hypertrophy, hydronephrosis, or pyelonephritis.

Foreign Bodies

It is always surprising, even to the urologist, how well the bladder will tolerate a foreign body without causing discomfort to the patient or producing serious pathologic changes. The list of various foreign objects removed from the bladder is quite enormous. Most of the foreign objects are introduced during abnormal sexual acts, mostly by young girls and the mentally disturbed.

Material overlooked at operation, broken-off fragments of catheters or drainage tubes, etc., make up a small proportion of all foreign bodies listed in literature. The patient frequently has no symptoms until the foreign object becomes encrusted and thus increases in size. Smooth objects such as a bead may remain in the bladder a very long time without becoming encrusted. Sharp objects embed into the wall or perforate forming vesicovaginal and vesicorectal fistulas.

Vesical Fistulas

Vesicovaginal Fistula.—Due to their close proximity, the most common fistulous communication is between the bladder and vagina. Vesicovaginal fistula is caused by obstetric injuries, pelvic operations, roentgen or radium therapy, inflammation and malignant neoplasms of urinary bladder, cervix and vagina. The size of the opening may vary from a pin point to several centimeters. The communication usually involves the posterior wall of bladder and upper anterior wall of vagina. The walls are discolored, undergo marked inflammatory changes, and in radium cases there is considerable sloughing. In long-standing cases, there may be eversion of the bladder mucosa.

Vesicoenteric Fistula.—Fistulous communication between the bladder and rectum, sigmoid, jejunum, ileum, or appendix occurs in both sexes but is more common in the male. These fistulas may result from trauma, inflammatory or neoplastic diseases, roentgen- and radium rays, or erosion of a vesical calculus. Severely inflamed diverticula of rectum or sigmoid may become adherent and extend through the bladder. Pelvic abscesses and gangrenous cystitis are frequent complications.

Vesicouterine Fistula.—The etiology of vesicouterine fistula is the same as that of the vesicovaginal type. The most common causes are neoplastic diseases and radiation therapy.

Neurogenic Dysfunction

Traumatic, neoplastic, inflammatory, and noninflammatory diseases of the nervous system

causing vesical dysfunction such as paralysis, atony, or hypertonicity of the urinary bladder are numerous. The lesion may be central or peripheral.

Central lesions that cause bladder dysfunction are traumatic and neoplastic diseases of the brain and cord, and inflammatory and non-inflammatory degenerative disease such as neurosyphilis (*tabes dorsalis*, paresis, and rarely *gumma*), multiple sclerosis, poliomyelitis, transverse myelitis, ataxic paraplegia, spina bifida, and, rarely, thrombosis and infarction. Central lesions usually cause the paralytic or the so-called cord type of the bladder. The mucosa of such relaxed bladders, when uncomplicated with inflammation, is pale and smooth, and shows threadlike trabeculation.

Peripheral nerve lesions causing neurogenic dysfunction of the bladder are found in spina bifida occulta, peripheral neuritis, infectious neuronitis and in some infectious diseases with high fever such as scarlet fever and diphtheria. Neurogenic dysfunction of the bladder has occurred in lead poisoning and alcoholic neuritis.

Amyloidosis

Ten cases of amyloidosis of the urinary bladder have been reported. The lesions appear as fungiform tumors with smooth or ulcerated surfaces. The amyloid is deposited in epithelial cells and submucous connective tissue and to a lesser degree in the muscularis and blood vessels.

Tumors

Leukoplakia.—The smooth, dead white, sharply demarcated patch known as leukoplakia represents an area of epidermoid transformation of the transitional cells of the bladder mucosa. It may be single, multiple, or, in very rare cases, involve the entire mucosa. Leukoplakia is definitely associated with chronic cystitis of long duration. In addition, syphilis, tuberculosis, and friction by calculi and foreign bodies have at one time or another been incriminated. Microscopic sections reveal two types of lesions. In one type there is a thickened layer of well-differentiated stratified squamous epithelial cells. In the second type the layer of squamous epithelial cells shows activity or proliferation of the basal portion. The nuclei may be elongated, hyperchromatic, and frequently show mitotic figures. Such lesions have been considered precancerous, thus supporting the popular belief that they give rise to malignant neoplasms. A few cases of squamous cell carcinoma associated with leukoplakia have been reported.

Endometriosis.—The presence of endometrial tissue in the urinary bladder produces lesions which at cystoscopic examination resemble tumors, cysts, or localized inflammation. The histogenesis of vesical endometriosis has not been established. The same theories of endometriosis of other organs and tissues may be applied to endometriosis of the bladder with the exception of Sampson's theory (see Chapter 39) which most investigators reject. The urinary complaints of patients of vesical endometriosis are cyclic. Pathologists seldom see the gross

lesions on the mucous surface of the bladder. Most of our knowledge of the gross appearance of endometriotic vesical lesions has been contributed by urologists. The lesions appear as reddish, bluish, or bluish-black elevations in which small cysts may be recognized. Their usual size is 1 to 2 cm. in diameter, but they may appear as tumors of several centimeters in diameter. The mucosa around and sometimes over the lesion is congested, edematous, and thrown into folds. During menstruation, the lesions are larger, more congested, bluish, and cystic. Active bleeding may be present. During the intermenstrual period, the lesions are smaller, yellowish-red, and may have a few bluish spots or cysts. Microscopically, isolated glands or groups surrounded by an endometrial type of stroma are seen. The structures lie in the tunica propria and muscularis. Either recent or old hemorrhage with blood pigment is usually present.

Etiology.—The etiology of most benign tumors is unknown. Certain benign tumors originate from embryonic cell rests. Chronic inflammation, excretion of carcinogenic chemicals, and virus infections have their proper place in the etiology of transitional cell carcinomas. The theory of chronic inflammation as a causative factor seems to be substantiated by the relatively frequent occurrence of carcinoma in extrophied bladders, in bilharzial infestation, and in certain types of cystitis. The incidence of cystitis, papilloma, and carcinoma in aniline dye workers and persons exposed to nitro and amino compounds (benzene, alpha and beta-naphthylamine, etc.), is significant. According to Evans'⁵² analysis, tumors appear in workers with carcinogenic chemicals after 6 to 20 years of exposure. Kerwin,⁵⁶ apparently stimulated by the work with epitheliotropic viruses in the production of warts and rabbit papilloma, is of the opinion that papillomas of the bladder may result from virus infection. Adenomas and adenocarcinomas undoubtedly originate from cell inclusions of urachus and cloaca. Some authors believe that adenocarcinoma may originate from metaplastic changes of cell nests of von Brunn and cystitis cystica (see page 610).

Benign Tumors.—The most common histologically benign tumor of the bladder is the *transitional cell papilloma*. Because about 50 per cent of the papillomas recur and have a poor prognosis, they will be considered with the group of malignant tumors. Other benign tumors collected from literature are *fibromas*, *fibromyomas*, *leiomyomas*, *rhabdomyomas*, *neurofibromas*, *ganglioneuromas*, *angiomas*, *myxomas*, *adenomas* (adenomatoid tumors), *mucinous cystadenomas*, *granular cell myoblastomas*, *dermoids*, *hamartomas*, and *enteric and neuroenteric cysts*. Most of the *fibromas* are symptomless; therefore, the great majority are incidental findings at necropsy. They are usually single, pedunculated, grow slowly, and are commonly located in the posterior wall, especially the trigone. They may undergo degenerative changes and become malignant. The *fibromyomas* and *leiomyomas* are also usually single and range in size from a few grams to 9,200 grams in one case.⁵⁹ Some of these tumors are polypoid. They are composed of interlacing and parallel-arranged smooth muscle

fibers with a varying amount of intervening fibrous tissue. Some resemble uterine leiomyomas. Most of the *rhabdomyomas* occur in children. They are somewhat loose, spongy growths frequently near or around the urethral canal. The nuclei of these tumor cells vary in size; the majority are large and surrounded by partly striated, poorly stained cytoplasm. In some areas the cytoplasm is clear and the nuclei appear to lie in spaces surrounded by cell membranes. *Hemangiomas* are rare and occur in children. *Myxomas* occur at any age but more frequently in children. They are pedunculated soft tumors covered with bladder mucosa. *Neurofibromas* are single or multiple tumors usually located in the trigone or bladder neck and occasionally associated with von Recklinghausen's neurofibromatosis. *Hamartomas* of the urinary bladder have been described; however, their histological structures do not seem variable enough to justify the term hamartoma. Grossly, they are small, elevated, red granular areas ranging in size from 1 mm. to 1 cm. in diameter. They occur on the dome of the bladder, the area derived from the cloaca. Microscopically, they are composed of papillary structures of delicate fibrous tissue. These papillary structures are lined with one to several layers of cuboidal epithelial cells. In the deeper parts of the tumor there are small tubules lined with cuboidal cells. They may contain smooth muscle fibers. *Adenomatoid tumors* occurring in young adults between 18 and 29 years of age have been described and their genesis elucidated by Friedman and Kuhlenbeck.⁶⁰ These tumors are usually sessile polyps or nodules which histologically have a renal tubular pattern. The tubules are lined with single rows of cuboidal or columnar epithelial cells similar to those lining the loops of Henle, distal or collecting tubules, or mesonephric ducts. The diagnosis of nephrogenic tumors of the urinary bladder is appropriate for these glandular tumors.

Malignant Tumors.—About 95 per cent of malignant neoplasms, including the histologically benign papillomas, are of epithelial origin. The great majority are composed of transitional epithelial cells resembling those of the bladder mucosa. Approximately 1 per cent of all carcinomas originate in the urinary bladder. They may occur at any age but seldom before the age of 50. The highest incidence is between the ages of 55 and 70. They are about four times more frequent in males than in females. They are more frequently found in the trigone, lateral walls, and often around the ureteral orifices. About 50 per cent occur in the trigone. The great predilection for these locations, the vicinities of inlet and outlet, suggests urinary irritants as factors in etiology of their development. Occasionally, transitional cell carcinomas are encountered in diverticula.

Grossly, there are three types: (1) soft, fungating, cauliflower-like, (2) firm, smooth, nodular type, and (3) rough, flat, and ulcerating.

The histologically benign papilloma is considered under the topic of malignant tumors for the following reasons: (1) it is impossible to designate which papilloma is benign with any degree of certainty; (2) more than 50 per cent of so-called benign papillomas recur; (3) about 75 per cent of the patients develop an exigent condition within 2 to 4 years; (4) the great majority of the specimens submitted for diagnosis are biopsies; (5) portion of tumor submitted may not reveal the true picture, whereas the deeper parts may reveal the malignant character; (6) adoption of grading by urologists. Although the histologic grading does not always prove to be a true measure of clinical or gross anatomical degree of malignancy, yet in the great majority of the cases it has proved to be very useful. It is well known that one area of a papillary tumor, especially the uppermost portion, may reveal a grade I malignancy, whereas the deeper parts may reveal a higher degree of malignancy. It must be emphasized that from a prognostic aspect, the presence or absence of muscle invasion is more important than the histologic grade of malignancy, the size and location of the tumor, and whether the tumor is papillary or nonpapillary. In grade I papilloma, the transitional cells are well differentiated, the nuclei are uniform in size and show little abnormality, mitotic figures are very scanty or seldom found, and infiltration of the underlying layers is always absent. Grade II papillary tumors show some pleomorphism and hyperchromasia of the nuclei. Mitotic figures, although not abundant, are quite readily found. Infiltration of the underlying layers may or may not be present. Grade III transitional cell carcinomas reveal a moderate degree of cellular anaplasia and pleomorphism with many mitotic figures. The muscularis is always infiltrated. The cells of grade IV carcinomas are markedly anaplastic and pleomorphic and seldom retain traces of transitional cell morphology of their parent cells.

The simple (so-called benign) transitional cell papillomas are pinkish or red-

dish, somewhat shaggy, villous tumors ranging in size from a few millimeters to several centimeters in diameter. They may be pedunculated, broad-based, or flat and lobulated. Some papillomas are firm or wartlike and usually of greater degree malignancy. They may be single or multiple and since about 50 per cent of the cases are multiple, the cystoscopist should carefully inspect all parts of the bladder mucosa. Papillomas are more frequently found in the trigone, lateral walls and often around the ureteral orifices. The typical simple papilloma (grade I) consists of many delicate papillae composed

fungating masses almost fill the entire bladder. Other gross types of carcinomas are flat, rough, nodular, firm, soft or friable and ulcerating. The cells of grades II and III carcinomas maintain a semblance of transitional cell character, whereas the cells of grade IV tumors are so highly anaplastic and pleomorphic that by their morphology alone one cannot recognize their origin.

Squamous cell carcinomas of the bladder are flat, slightly elevated, ulcerating, highly infiltrating tumors. The margins of these tumors are firm and everted. They are composed of irregular sheets and anastomosing cords of squamous



Fig. 497.—Papillary transitional cell carcinoma of the urinary bladder.

of a central fibrovascular core surrounded by layers of well-differentiated transitional cells. A well-defined basement membrane separates the cells from the fibrovascular core. The outer layers of cells are parchmentlike and in the deeper layers they may be polygonal, cuboidal, or columnar. Papillary and nonpapillary transitional cell carcinomas of grades II, III, and IV develop from the same locations as the simple papillomas (grade I). From these regions they spread to all parts of the bladder, and not infrequently large

epithelial cells which in some tumors show keratinization and pearl formations. Intercellular bridges may sometimes be present. A characteristic always encountered in this neoplasm but absent in transitional cell carcinomas is reactive fibrosis. Some transitional cell carcinomas develop squamous cell metaplasia.

Adenocarcinoma of the bladder is rare, and is probably less frequent than reports indicate. Some of the tumors resemble those of the prostate gland, others resemble mucinous adenocarcinomas of the colon. It is well known that both prostatic and rectal carcinomas invade the bladder; therefore, one must be cautious in deciding the primary site. Adenocarcinomas of the bladder originate from enteric rests,

remnants of cloaca or urachus, and probably from periurethral glands around the vesicle neck. It is doubtful whether transitional epithelium ever suffers glandular metaplasia. However, some maintain that transitional cell nests of von Brunn, which are transformed into cysts in cystitis cystica (see page 610), may also undergo metaplastic changes and develop areas of cystitis glandularis (see page 610), which may undergo malignant changes and be transformed to adenocarcinoma. The tumors are usually flat, elevated, ulcerated, and contain rolled-over borders. Some are nodular, villous, and cystic. Adenocarcinomas are more likely to develop in extraprostatic bladders.



Fig. 498.—Firm nodular carcinoma involving the trigone, causing obstruction and hypertrophy of the bladder, obstruction of ureter, and eventual hydroureter and hydronephrosis.

Metastasis and Complications.—Bladder carcinomas spread by contiguity to the adjoining structures such as rectum, sigmoid, prostate, ureter, vagina, uterus,

broad ligaments, and bones. Bladder muscle penetration with neoplastic cells is an important criterion in prognosticating local or distant metastasis. It is therefore important that the cystoscopist obtain a deep biopsy to include the muscular coat of the bladder. Distant metastasis by lymph and blood stream routes involve pelvic and abdominal lymph nodes, lymph nodes of thorax and neck, pelvis, sacrum, spine, lungs, peritoneum, pleura, liver, brain, and skin. Complications are marked hematuria, hydronephrosis due to obstruction, pyelonephritis due to ascending infection, and vesicorectal, vesicovaginal, and vesicoenteric fistulas.

Implants.—Metastasis of transitional cell carcinoma of the renal pelvis or ureter by implantation on the bladder mucosa has been repeatedly demonstrated. Such metastasis may at times be extensive. It is, therefore, important that pyelograms be made whenever a bladder tumor is found. It is also advisable to examine the ureter when performing a nephrectomy for transitional cell carcinoma of the renal pelvis.

Sarcoma.—The various sarcomas recorded in literature are *myosarcomas* (leio- and rhabdo-), *myxosarcomas*, *osteochondrosarcomas*, *lymphosarcomas*, *plasmacytomas*, and *Kaposi sarcoma*. All of these are rare. They are predominant in the very young and the aged. The most common locations are in the vesical neck and lateral and posterior walls. They are soft, friable, polypoid or irregular, sometimes nodular, and frequently necrotic and hemorrhagic. They are highly malignant, rapidly infiltrating, and metastasize to any part of the body. Patients usually die within six months to one year after they are discovered.

Cytologic Diagnosis of Bladder Carcinoma.—Cytologic study of urinary sediment by staining rapidly fixed smears has gained proponents in the recent years. Interpretation of such smears requires considerable time and, as a prerequisite, it requires special training. The constant exfoliation of urinary tract epithelium is increased when inflammation, lithiasis, and neoplasm exist. Various investigators have proved that repeated examination of urinary sediment revealed neoplastic cells before a neoplasm could be detected cystoscopically or roentgenographically if a tumor involved the kidney pelvis.

The morphology of normal exfoliated epithelial cells of the urinary tract varies. The epithelium of the renal pelvis, urinary bladder, and posterior urethra is transitional. The superficial exfoliated cells are elongated, cuboidal, or somewhat flattened. The middle cells are conical or club-shaped and the basal exfoliated cells are rounded. Binucleated and multinucleated forms are occasionally encountered. In the female urine squamous epithelial cells may be present. The chromatin of the nuclei of all of these cells

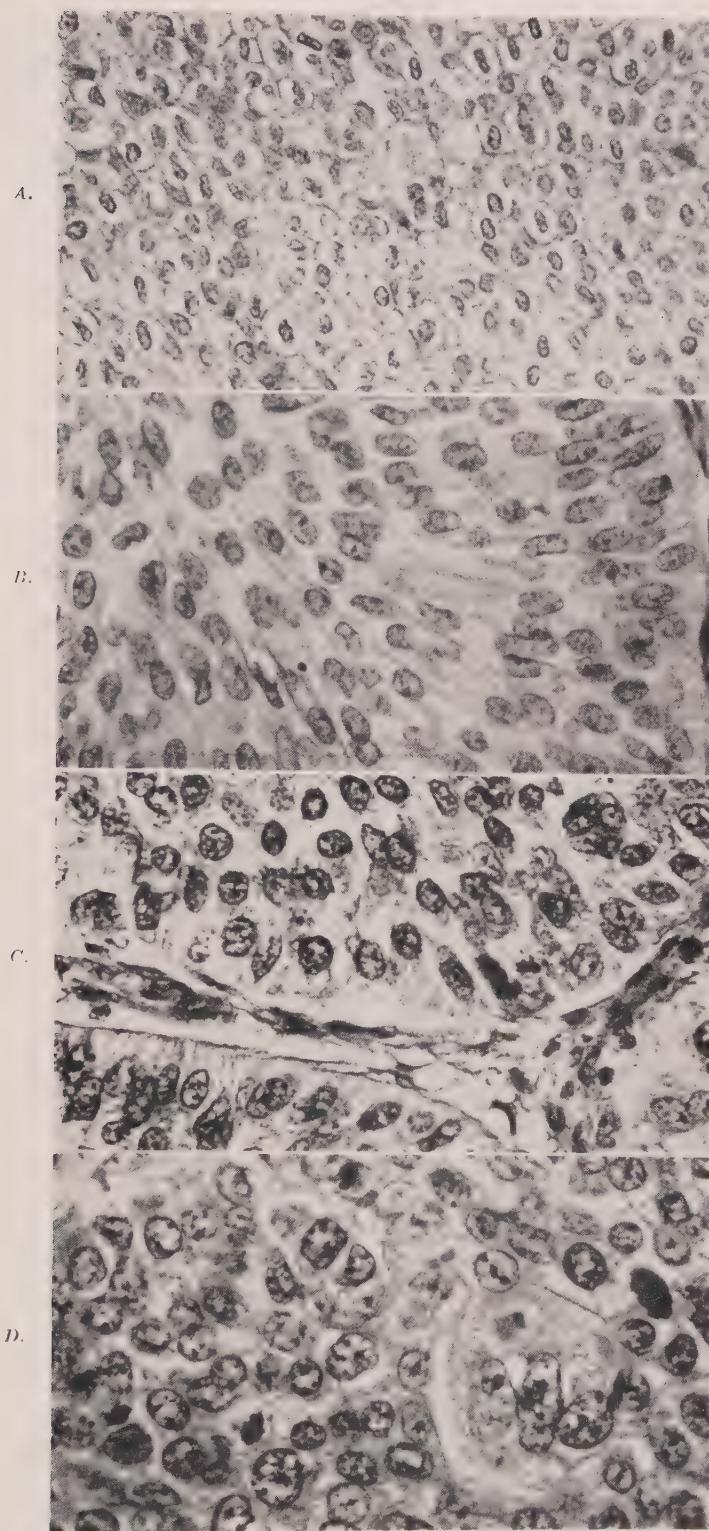


Fig. 499.—Urinary bladder: *A*, Transitional cell papilloma, grade I; *B*, transitional cell carcinoma, grade II; *C*, grade III; *D*, grade IV.

is evenly distributed and there is a uniform nuclear-cytoplasmic ratio.

The criteria for identifying neoplastic cells are quite definite to the experienced. The cells frequently occur in groups and vary somewhat in size and shape. The cytoplasm is hazy and the cell borders are indistinct or absent. Nuclear aberration is quite distinct. The nuclei are hyperchromatic and their chromatin is of unequal size, heavily clumped, or there may be heavy strands. The chromatin in some nuclei is condensed at the periphery. The nuclear-cytoplasmic ratio is definitely increased.

Harrison and associates reported demonstrable neoplastic cells in the urine in all of their 67 cases of vesical carcinoma.

URACHUS

The allantoic duct which opens into the apex of the bladder involutes to form a cord known as the urachus. Occasionally, the urachus remains patent and forms a tube opening at the umbilicus. The urachal canal almost never obliterates but retains a bore of less than 1 mm. in diameter. In about two-thirds of adults, the lumen is separated from the bladder by a transverse fold, and in the remaining third the lumen is patent or partly closed. The anomalies of the urachus consist of various forms of patent urachus, including the urachal fistulas and cysts. The *umbilico-uracho-cystic fistula* develops as a result of nondescent of the bladder and frequently a granulation tissue tumor forms in the umbilicus. The *uracho-umbilical fistula* may be congenital or acquired. The congenital type communicates with the umbilicus and not the bladder. The acquired umbilico-urachal fistula results from increased intravesical pressure, usually at the junction of the bladder and urachus. Urine escapes between the transversalis fascia and peritoneum and may perforate through the floor of the umbilicus. *Urachal cysts* are the result of closure of both ends of the urachus. They may reach enormous size. One case was reported to contain 52 liters of fluid. Urachal cysts may rupture at the umbilicus or into the peritoneum but very seldom into the bladder. The most common tumors of the urachus are adenomas and mucoid adenocarcinomas. They usually develop at the apex of the bladder, either outside of the wall of the bladder or on its outer muscular layer. Adenocarcinoma of urachus may involve both the anterior abdominal and the bladder walls. They occur most frequently in adults and about 80 per cent of the recorded cases were in males.

PROSTATE GLAND

Inflammation

Acute Prostatitis.—Acute inflammation of the prostate gland is usually due to extension of posterior urethritis, epididymitis, cystitis, and pyelonephritis. It occasionally occurs in pyemia and septicemia. The most frequent microorganism that invades the gland is *Neisseria gonorrhoea*, but other bacteria (staphylococci, strepto-

cocci, *Escherichia coli*, diphtheroids, etc.) may attack. Various forms of trauma and infection by catheterization are infrequent agents in causing acute prostatitis. Acute catarrhal prostatitis is almost always associated with acute posterior urethritis. Suppurative prostatitis is characterized by distention of the tubules by purulent exudate which may obstruct the ducts and result in the formation of an abscess. In acute diffuse prostatitis there is extensive hyperemia, edema, and diffuse inflammatory cellular infiltration of the stroma.

Chronic Prostatitis.—Chronic inflammation of the prostate gland is very common and has been delegated an equally important role with teeth and tonsils in harboring foci of infection causing arthritis, myositis, neuritis, and iritis. Allergic manifestations have been attributed to chronic prostatitis. Asthma, dermatitis, and pseudoangina pectoris have been cured by adequate treatment of prostatitis. About 70 per cent of necropsy prostates of men past 50 years of age reveal inflammatory changes. The etiological agents of chronic prostatitis are the same as those that cause acute prostatitis, although one must admit that in some types of chronic prostatitis the etiology is unknown. Corpora amylacea or prostatic calculi may cause obstruction and stasis of secretion leading to secondary inflammatory changes. A great variety of cocci and bacilli are isolated from the chronically inflamed prostates; however, quite frequently cultures of such prostates yielded no bacterial growth. Chronic suppurative inflammation may cause obstruction of the ducts and dilatation and rupture of glands, often resulting in abscess formation. The most common form of chronic prostatitis reveals diffuse, patchy or very discrete foci of lymphocytic and plasma cell infiltration with some fibrocytic proliferation. Many acini are filled with desquamated epithelial cells, some leukocytes, and cellular debris. Some acini become markedly dilated due to intraluminal occlusion of ducts by various cellular elements and corpora amylacea or extraductal pressure by fibrous tissue proliferation.

Cavitary or Diverticular Prostatitis.—Diverticula or cavities may develop in any type of prostatitis in which there is stagnation of exudate in ducts and acini. Prolonged stagnation causes reactive fibrous tissue proliferation.

which constricts the ducts. Acini dilate and intra-acinar septa become thin and break down resulting in formation of cavities. Prostatic diverticula may develop in cases of urethral stricture due to dilatation of prostatic ducts opening into the posterior urethra as a result of back pressure. Urine may enter the cavities and salts may precipitate to form calculi.

Granulomas.—*Tuberculosis* is the most common granuloma of the prostate compared with the rare syphilitic, blastomycotic, and coccidioidomycotic granulomatous inflammations. The great majority of cases of tuberculous prostatitis have been observed in young adults with urogenital tuberculosis.

Parasitic Infection.—*Echinococcal* and *bilharzial* infections are rare. Infestations with *Trichomonas vaginalis* would be encountered more often if a wet preparation of prostatic fluid expressed by massage were examined microscopically soon after collection.

Calculi.—The etiology of the development of prostatic calculi is not definitely known. Calculi are encountered in nodular hyperplasia, acute and chronic prostatitis, and occasionally in carcinoma. They occur in about 20 per cent of the glands in men past 50 years of age. There are two types of calculi: (1) *endogenous or true prostatic calculi* which are formed from the components of the prostate, and (2) *exogenous or false calculi* which are of urinary origin. A corpus amylacea forms the nucleus of an endogenous calculus. When the corpora amylacea obstruct the acini, they become closed cavities and prostatic secretion stagnates and becomes infected. Such secretion irritates the acinar epithelium. Inorganic salts of calcium phosphate and carbonate impregnate and precipitate around the corpora amylacea converting them into various sized calculi. Other endogenous calculi may form about a nucleus of compact cellular debris, blood clots, or necrotic tissue. There may be one to several hundred in one gland. They vary in size from 1 mm. to 5 cm. in diameter. There may be one in a dilated acinus or duct or several packed in a cavity. They may be round, ovoid, or triangular, and when grouped together they may have faceted surfaces. Their color varies from white or gray-white to various shades of brown. Some are very firm and brittle whereas others are somewhat plastic. *Exogenous calculi* occur less frequently and are always brittle and rough. The type of calculus may be determined by chemical examination of the nucleus. The nucleus of an exogenous calculus contains ureates and earthy phosphates whereas the nucleus of an endogenous calculus is composed of organic material. Prostatic calculi are frequently seen in roentgenograms of the pelvis.

Thrombosis and Infarction.—A common necropsy finding, especially in bedridden patients, is thrombosis of the periprostatic venous plexus. It has been doubted whether thrombi of these veins ever break loose to cause pulmonary embolism. However, in one of the author's cases, the only source of multiple infarcts in the lungs and ultimate fatal pulmonary embolism in a man aged 34 was massive thrombosis of the periprostatic venous plexuses. The thrombosed areas usually organize and form phleboliths, which are often seen in roentgenograms. Infarcts

may be due to vascular changes associated with arteriosclerosis, hypertension, periarteritis, and occasionally may be of embolic origin as in bacterial endocarditis. Local changes due to trauma by passage of sounds, catheters, cystoscopes, massage of prostate and transurethral prostatic resection have initiated infarction. Impacted feces and passage of rectal tubes have been recorded as causing sufficient trauma to initiate infarction. The glands around the infarcts frequently undergo squamous cell metaplasia. Recent investigations indicate the possible role of estrogens of adrenal origin in stimulating squamous cell metaplasia. Squamous cell nests remain in the zone of healed infarct and are occasionally misinterpreted as carcinoma.

Cysts.—Cysts of the prostate may be congenital or acquired. The congenital cysts are symmetrical and associated with other abnormalities such as patent urachus and spina bifida. The Müllerian duct cyst is usually retroprostatic. The Müllerian duct, if it were patent, would extend from the appendix testis in a groove between testicle and epididymis, up the spermatic cord, lie between vas deferens and bladder where it would join the duct from the opposite side. It would then become incorporated in musculature of bladder wall, pass through the prostate, and end in the utricle. Thus it is understandable that such cysts, forming from abnormal remnants of the Müllerian duct, may form anywhere along its course. Müllerian duct cysts vary in size from a small dilatation of the utricle to huge masses containing several liters of clear straw-colored to chocolate-colored fluid. The wall of the cyst is composed of a laminated collagenic fibrous tissue lined by flat or low cuboidal epithelial cells. Acquired forms are retention cysts and echinococcal and bilharzial cysts.

Hyperplasia.—Enlargement of the prostate gland is commonly termed benign hypertrophy, although histologically hyperplasia predominates. The causes of enlargement of the prostate have not been established. Five theories are usually discussed: (1) they are benign tumors (adenomas), (2) they are akin to leiomyomas, (3) infection, (4) arteriosclerosis, (5) endocrine disturbance. The first four theories may be dismissed since there is no experimental evidence to substantiate their claim. The endocrinopathic mechanism causing enlargement of the prostate is not entirely clear, but enough evidence of hormonal imbalance has accumulated to warrant its consideration. It is common knowledge that eunuchs and castrates do not develop enlargement of the prostate. Hypophysectomy leads to atrophy of the testes and prostate, whereas orchidectomy is followed by atrophy of the prostate and enlargement of the hypophysis. The production of androkin, a male sex hormone

similar to ovarian theelin, in the testicle is regulated by the anterior pituitary. Hyperfunction of the pituitary, demonstrated by injection of anterior pituitary-like substance, stimulates overproduction of androkin and causes enlargement of the prostate. A second hormone, contruin (inhibin), is postulated on experimental basis as being produced by the germinal cells of the testicle. Contruin inhibits excess secretion of pituitary hormone, but

The normal weight of the prostate gland is about 20 grams. The enlarged prostate is usually two, three, or four times larger than normal but is seldom more than 200 grams. Ockerblad⁹³ removed an enlarged prostate weighing 820 grams. Hyperplasia usually involves the middle and lateral lobes, seldom the anterior lobe, and almost never the posterior lobe in which development of carcinoma is frequent. Simonds,⁹⁴ Lowsley,⁸⁸ and others have convincing evi-



Fig. 500.—Hyperplasia of the prostate gland with obstruction of the urethra by large middle lobe; hypertrophied bladder with cellules and diverticula.

when decreased function of the germinal cells occurs there is a lessened inhibition of the pituitary, which leads to increased activity, thus producing excess androkin and consequent enlargement of the prostate. Huggins⁸⁹ believes that hyperplasia of the prostate is made up of multiple neoplastic nodules produced by androgen stimulation over a period of years in a gland that has a low threshold for androgens.

dence that glandular hyperplasia of the prostate begins in most instances in the submucous (subcervical and subtrigonal) groups of tubules.

Grossly, the enlarged gland is smooth or nodular, firm, and somewhat elastic or of rubbery consistency. The appearance of the surfaces made by sectioning depends upon whether the greatest amount of hyperplasia involves the glands or the fibromuscular tissue. If the hyperplasia is

more glandular, the cut surface reveals many various-sized nodules, some of which are well circumscribed and surrounded by pearly-white fibromuscular tissue. Some of the nodules have a honeycombed architecture. The cut surfaces of an enlarged prostate with predominance of glandular hyperplasia become readily moistened with a milky fluid. Cysts are common and some of these may contain white or amber-colored corpora amylocaea or seed calculi. If the hyperplasia is predominately of fibromuscular tissue, the cut surfaces are pallid, glossy, somewhat homogeneous, and very little milky fluid can be expressed.

and very few or no glands. As the fibromuscular tissue increases in amount it incorporates the glands, which also take part in the hyperplastic process, and, as a rule, overtakes the hyperplasia of the fibromuscular tissue. The acini are increased in number and size. Many undergo dilatation and invagination. The tortuous and dilated glands contain intraluminal villous projections. Some of the glands become cystic. The glands as a rule are lined with single rows of columnar epithelial cells, but it is not uncommon to find several rows. Some of the small acini are lined with cuboidal cells. The lumina contain desquamated epithelial cells, gran-



Fig. 501.—Diffuse nodular hyperplasia of the prostate with obstruction of urethra: hypertrophy and dilatation of the bladder; large diverticulum at dome of bladder.

In recent years, studies have shown that prior to hyperplasia of the periurethral glands there is a diffuse or nodular fibromuscular hyperplasia. Fragments of prostate tissue removed transurethrally frequently reveal hyperplastic fibrous tissue, hypertrophied muscle fibers,

ular material, some leukocytes, and uncommonly corpora amylocaea. The hyperplastic fibromuscular stroma is frequently infiltrated with lymphocytes which many interpret as an inflammatory reaction. It has not been convincingly proved that the presence of lymphocytes in a hyperplastic

prostate gland is an indication of inflammation. However, chronic prostatitis does exist in some of the hyperplastic glands. The glandular hyperplasia may be so pronounced that it not only resembles a nodular adenoma but may appear as an adenocarcinoma to the inexperienced.

The chief complications produced by the enlarged prostate are those of obstruction of outflow. There is retention and overflow of urine and the bladder is never completely emptied. Micturition is accomplished with difficulty, due to disorganization and stretching of the muscle fibers of the urethral sphincter, causing hypertonus which prevents voluntary relaxation but does not prevent leakage. The pressure tends to push the enlarged prostate against the urethral wall, thus enhancing the obstruction. Obstruction is usually followed by hypertrophy and dilatation of the urinary bladder with formation of cellules and diverticula. The dilatation progresses beyond the urinary bladder and extends to involve the ureter (hydroureter) and kidney (hydronephrosis). If infection supervenes, as it commonly does, cystitis and pyelonephritis follow.

Tumors

Benign Tumors.—If the nodules of nodular hyperplasia of the prostate are considered as tumors (as some believe), then benign tumors are very common. They might be termed adenomas, fibroadenomas, fibromyomas, fibromas, or leiomyomas. Differentiation of hyperplasia from a neoplasia is at times difficult. While some of the circumscribed nodules of the enlarged prostate are akin to tumors, in the author's opinion they should not be designated as neoplasms. Some of the reported adenomas were actually circumscribed areas of glandular hyperplasia and likewise many of the recorded leiomyomas were instances of fibromuscular hyperplasia. Therefore, in the author's opinion benign tumors of the prostate are rare. Kaufman and Berneike¹⁰³ recorded 38 cases of leiomyomas. The average age was about 60. The tumors weighed from about 15 to 1,450 grams. The writer has seen two such tumors. They are firm, rubbery, yellowish-white, and homogeneous. Microscopically, they reveal interlacing whorls of smooth muscle with very little intervening fibrous tissue.

Carcinoma.—The etiology of carcinoma of the prostate gland is unknown. Predisposing causes such as hyperplasia, atrophy, and regeneration, and exciting causes such as chronic prostatitis and hyperandrogenism have been considered by various investigators. The results of endocrinological

experiments seem to imply an estrogen-androgen imbalance as the most important condition for neoplasia.

Carcinoma of the prostate seldom occurs before the age of 50. The incidence increases with age. It is encountered in 10 to 15 per cent of necropsies of men past 50 years of age. Approximately 15 to 20 per cent of hyperplastic nodular prostates harbor carcinoma, whereas 50 per cent of carcinoma of the prostate are associated with nodular hyperplasia. The occult type of carcinoma excites no symptoms and the neoplasm is discovered during microscopic examinations. Carcinoma may originate in any subdivision of the prostate but about 75 per cent arise in the posterior lobe.

Grossly, the neoplastic prostate may be large, normal size, or smaller than normal. It is very firm, often nodular, and contains a thick tough capsule. When the cancer has advanced through the capsule, the gland becomes anchored to the surrounding structures and excision is extremely difficult. When sectioned, the gland imparts a sensation to the knife as if cartilage or tough fibrous tissue is cut. The cut surface is dry, fibrous, homogeneously pallid, and often contains irregular yellowish areas.

Carcinomas of the prostate vary greatly in structure. There are few distinct types. Usually there is a mixture of scattered groups of glands, compact small acini, scirrhous and medullary forms. About 2 per cent are squamous cell carcinomas or a mixture of glandular structures and squamous cells. Structural types or even grading according to degree of malignancy have doubtful clinical implications. Most of the adenocarcinomas are composed of small acini lined with single rows of small or medium-sized cuboidal or low columnar epithelial cells, having pale, slightly granular, or clear cytoplasm. The nuclei are small, round, and uniform in size. Anaplasia or pleomorphism and mitotic figures are scarce and frequently absent. Nests of small acini either scattered or compact invade the stroma. Scirrhous tendency similar to the breast carcinoma is a frequent occurrence. There are scattered irregular cords of small cells, tiny acini, isolated clusters of cuboidal cells lying in a rather abundant fibrous tissue stroma. In the medullary types, sometimes termed

carcinoma simplex, there are solid nests and bands of rounded and cuboidal cells and the stroma is reduced to a trace.

The surprising, somewhat apparent maturity of the neoplastic cells in many carcinomas of the prostate, the lack of cytologic criteria of malignancy, perhaps seen in no other organ, have puzzled many pathologists. Cellular pleomorphism is the exception. Mitotic division is minimal and often absent in many sections. What, therefore, are the criteria of malignancy in the prostate? We apparently must rely on the architectural deviation. The sections are, therefore, best studied under low magnification. With this magnification, the atypical pattern of the acini, the absence of their usual convolutions, and the haphazard distribution stand out in contrast to the normal residual parts.

Transurethral fragments have sometimes been difficult to study because of the coagulation effect of the electric current causing distortion of cells. It is the rule of the author to select the larger chips and cut many cross sections for histologic preparation. Such preparations always contain intact deep structures. Benign squamous cell metaplasia in areas of healed infarcts or in healed areas of previous transurethral resections have been misinterpreted as malignancy. Errors have likewise been made in interpreting nests of polygonal cells from periurethral ducts frequently present in transurethral fragments.

Metastasis occurs in about 50 per cent of the cases. The urinary bladder is invaded in about 35 per cent of the patients. Carcinoma of the prostate is prone to metastasize to the vertebrae, pelvic bones and, less often, to other bones. Pain in the back or hips due to metastasis may be the first symptom in occult carcinoma. According to Graves, Warren, and Harris, the route of metastasis to the spine is by way of perineural lymphatics; however, Batson has convincingly demonstrated that metastasis is hematogenous. The hematogenous route involves the vertebral veins which are connected with the veins of the seminal vesicles. There is early and frequent invasion of the seminal vesicles, especially when carcinoma originates in the posterior lobe. Lymphatic spread may be quite early and occasionally very extensive.

Lymph node invasion involves the pelvic, periaortie, inguinal, mediastinal, and supraclavicular lymph nodes. Spread to the lungs and liver usually indicates hematogenous metastasis.

Sarcoma of the prostate is rare. It occurs at any age but is much more frequent in the young. The author has seen a fibrosarcoma in a 5-year-old boy. Fibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, angiosarcomas, and lymphosarcomas are recorded in the literature.

Cytologic diagnosis of carcinoma of the prostate by rapid fixation of wet smears of prostatic fluid or urine after digital massage is becoming more popular. Whereas early investigators considered the procedure highly unreliable, more experience has resulted in a greater degree of accuracy so that recent reports on this diagnostic procedure are quite convincing. The neoplastic cells in properly prepared smears are pleomorphic, the nuclear-cytoplasmic ratio is disturbed, the nuclei are hyperchromatic, cell borders are absent or indistinct, whereas the nuclear borders are sharp. Very often the cancer cells occur in clusters and the nuclei in these clusters vary in size, whereas the nuclei in clusters of normal cells are uniform in size and staining reaction. Peters and Benjamin studied the cytologic changes of cancer cells in patients receiving estrogens and concluded that the Papanicolaou method may be used as an additional guide to the response of hormonal therapy in carcinoma of the prostate.

Endocrine Therapy.—Administration of estrogens and orchidectomy are established therapeutic procedures in the management of patients with carcinoma of the prostate. Orchidectomy is not performed as frequently as in former years. Stilbestrol may induce degenerative changes of neoplastic cells in the prostate and in the metastases. The degenerative changes are characterized by disappearance of nuclear membranes and nucleoli, diminution and disappearance of mitotic figures, loss of staining quality of cytoplasm, rupture of cell membranes, and clumping of nuclei. Stilbestrol may also cause squamous cell metaplasia of neoplastic cells in the prostate and osseous metastases.

Acid phosphatase is present in the prostate gland, blood, and urine. By special histologic technique it has been demonstrated in the normal and neoplastic cells. In carcinoma of the prostate, especially when there is metastasis, the concentration of acid phosphatase is increased in the blood and in the urine. Serum acid phosphatase may be increased compared with the original level when the carcinoma was discovered and provide evidence of metastasis before it is demonstrable roentgenologically. There is a drop of serum acid phosphatase about a week after therapeutic surgical castration and 2 or 3 weeks after initiating estrogen therapy. The cause of this drop is not clearly understood. It is known that androgens stimulate and estrogens inhibit secretion of the prostate gland. Apparently estrogens inhibit production of acid phosphatase. Determination of phosphatase activity of treated and untreated carcinoma reveals that phosphatase activity of treated carcinoma is greatly reduced. No other

metastatic lesion in bone yields increased serum acid phosphatase; therefore, this chemical laboratory procedure is an important differential diagnostic aid.

PENIS

Phimosis is a condition in which the preputial orifice is too small to permit retraction of the prepuce behind the glans. It is independent of inflammation of the foreskin. An acquired phimosis may result from inflammation, trauma, or edema which narrows the preputial opening so that the prepuce cannot be retracted. A long or redundant foreskin is not uncommon and should not be considered as phimosis if it can be retracted. However, congenital redundant foreskins may become adherent or develop phimosis if secretions or foreign material are allowed to collect. Congenital phimosis predisposes to development of preputial calculi and squamous cell carcinoma. Paraphimosis is a condition in which the retracted prepuce cannot be reduced. It is usually a complication of gonorrhea, chancre, chancroid, balanitis, or trauma.

Hypospadias is a congenital defect in which the urethral meatus is present on the under-surface of the penis. It is due to imperfect closure of the urethral groove. The arrest may take place anywhere along the urethral groove, thus resulting in (1) glans hypospadias, (2) penile hypospadias, and (3) perineal hypospadias.

Epispadias is a rare form of congenital defect in which the urethral meatus is located at the upper surface of the penis. Its incidence is one in 50,000 newborn infants and is frequently associated with cryptorchidism, extrophy of the urinary bladder, or absence of the prostate gland.

Inflammation

Syphilis.—The common site of a hard chancre is on the glans near the frenum or on the inner surface of the prepuce. It may also occur within or at the side of the urethral meatus or, rarely, on the shaft. See discussion on page 271.

Herpes Progenitalis.—Herpes progenitalis is characterized by development of a group of vesicles on the glans or prepuce. The surrounding tissue is inflamed. The vesicles rupture, and small discrete or confluent ulcers develop which heal within a short time.

Granuloma Inguinale.—Granuloma inguinale usually begins in the inguinal region and spreads to the perineum, scrotum, and penis. Nodules and serpiginous ulcers develop on the prepuce, which spread to the glans and the shaft. See discussion on page 289.

Lymphogranuloma Venereum.—Lymphogranuloma venereum is a specific venereal disease caused by a filtrable virus. The primary lesion may be single or multiple herpetic vesicles, single or multiple papules, or a hard deep nodule appearing two to seven days after exposure. It appears on the coronal sulcus, glans, prepuce, or urethra. The inguinal lymph nodes usually begin to enlarge within ten to thirty days after the appearance of the primary lesion. See discussion on page 291.

Fusospirochetosis.—Erosive and gangrenous balanitis is a disease comparable to Vincent's angina and is caused by a fusiform bacillus (*Vibrio*) and a spirochete. See discussion on page 287.

Plastic Induration of Penis (Peyronie's Disease).—Peyronie's disease is a fibrosis of the penis involving Buck's fascia and the sheath of one or both corpora cavernosa. The etiology is unknown. Scott and Scardino¹¹² believe the fibrosis is due to vitamin E deficiency. The disease is more common than the reports in literature indicate. About 5 to 10 per cent of prostatic cases reveal mild lesions. Two types are described: (1) thickening and contracture of the median septum, and (2) localized nodules or indurated thickened areas involving the sides and underportion of the sheath of the corpus cavernosum. Microscopically, there is a scanty cellular fibrous tissue in which there are few blood vessels and mild evidence of inflammation. The lesion often resembles scar tissue. Occasionally the fibrous tissue undergoes ossification.

Erythroplasia (Queyrat).—This is a pinkish, precancerous or Paget-like lesion which usually involves the glans, but may occasionally occur on the coronal sulcus or prepuce. The lesion is shiny, pinkish-red, flat, faintly elevated, and sharply marginated. The surface is smooth, slightly eroded, "velvety," more firm than the surrounding normal tissue, quite pliable and with definite evidence of fixation to the underlying tissue. Microscopic sections reveal erosion of the epidermis with acanthosis and elongation of the rete pegs which are psoriaform and frequently attached to each other. The subepidermal layer of the cutis is edematous, contains many dilated vessels, and the inflammatory cellular infiltration is rich with plasma cells.

Tumors

Benign squamous cell papillomas under various names are common; however, benign mesodermal tumors are rare. Lipomas, fibromas, and angiomas have been reported.

Condyloma acuminatum, incorrectly termed venereal wart, is a raspberry- or cauliflower-shaped tumor usually located on the sulcus. The tumor may be a single papilloma or there may be multiple or conglomerated papillomas. These tumors are frequently found associated with or following various inflammatory diseases of the penis. A viral etiology cannot be excluded. Microscopically, there is acanthosis in the gourd-shaped processes.

Verruca is an ordinary squamous cell papilloma revealing hyperkeratosis and thus differing from a single condyloma in which the epithelium is piled up in the middle layer (acanthosis).

Squamous Cell Carcinoma.—In the United States, less than 2 per cent of all skin cancers arise in the penis. The incidence in other parts of the world are as follows: China, 18.3 per cent (Ngai¹¹⁶); continental Europe, 4.9 per cent; Great Britain, 1.27 per cent (Andrews¹¹⁵). In this country it is about three or four times more frequent in the Negroes. The greatest incidence is between the ages of 45 to 60.

Rare cases in childhood and early adult life have been reported.

One would not exaggerate by stating that the presence of a foreskin is a predisposing cause for squamous cell carcinoma of the penis since without this structure the incidence is insignificant. In India, the Mohammedans who practice circumcision as a religious rite never develop carcinoma of the penis, whereas the Hindus, who do not circumcise, have about a 10 per cent incidence. Only one case of carcinoma of the penis has been reported in a Jew. The exciting causes of this neoplasm are due to irritation of retained smegma, phimosis, and trauma.

The location of the neoplasm according to frequency is (1) frenum and prepuce, (2) glans, and (3) coronal sulcus. The tumors may be papillary or flat, ulcerating lesions. They grow slowly, and, histologically, they are of low-degree malignancy. Metastasis in the inguinal lymph nodes occurs in about 30 per cent of the cases. Visceral metastasis is extremely rare.

Adenocarcinoma.—Adenocarcinomas are very rare. They originate from the glands of Littré, the lacunae of Morgagni, and Cowper's glands. Several mucoid adenocarcinomas of Cowper's gland have been reported.

Sarcoma.—The types of sarcomas reported in the literature are fibrosarcomas, Kaposi sarcoma, endothelioma, and malignant melanoma.

URETHRA

Diverticula.—Diverticula are fairly common in the females but rare in the males. They may be congenital or acquired. Congenital true diverticula, arising from the periurethral glands, always occur on the ventral wall of the anterior urethra, whereas acquired diverticula develop in the posterior urethra. The acquired diverticula are due to inflammation or trauma. They may result from strictures, ruptured periurethral abscess, and urethrolithiasis. They are usually lined with transitional epithelium, but occasionally there is squamous cell metaplasia.

Prolapse of urethra occurs almost exclusively in the females. The prolapse usually involves the entire circumference and the lumen is located in the center. Pressure and infection produce vascular engorgement and acute inflammation. The lesion must be differentiated from a caruncle, polyp, urethrocele, condyloma, and carcinoma.

Gonococcal Urethritis.—Acute urethritis may be due to a variety of bacteria. Gonococcal urethritis in the male, as a rule, involves the portion of urethra anterior to the triangular ligament. The distal portion is usually not involved because the gonococci seldom penetrate the stratified squamous epithelium which lines this portion. The gonococci multiply on the intact mucosa of the proximal portion of the anterior urethra. It is the endotoxin of the dead bacteria that mainly excites the purulent inflammation. The purulent exudate develops within three to eight days. The exudate is rather viscid, yellowish or greenish-yellow, and microscopically reveals polymorphonuclear neutrophiles, many of which have phagocytosed

gram-negative diplococci. When the periurethral glands are invaded by the bacteria, the purulent exudate becomes copious. Ulceration of the mucosa and periurethral glands favors lymph and blood stream invasion. The regional lymph nodes, particularly the inguinal group, are frequently involved. Copelli and Gennari¹²¹ have demonstrated that gonococcemia exists in all cases of gonococcal urethritis. The infection may clear spontaneously within two to four weeks or may become chronic. The complications of acute gonococcal anterior urethritis are balanitis, balanoposthitis, periurethral abscess, posterior urethritis, prostatitis, prostatic abscess, cowperitis (Cowper's glands), seminal vesiculitis, epididymitis, cystitis, and systemic involvement affecting joints, tendon sheaths, endocardium, etc.

Nonspecific Urethritis.—Trauma, injection of chemical irritants, masturbation, coitus (in which female partner may suffer a nonspecific vaginitis), redundant foreskin, and "pin-hole" meatus are causes of nonspecific urethritis. This infection may also be associated with pyelonephritis, cystitis, and prostatitis-seminal vesiculitis. Various bacteria have been isolated and among these, staphylococci, streptococci, and colon bacilli predominate.

Urethral and Periurethral Abscesses.—Abscesses within and contiguous to the urethra are infrequent. They are usually complications of gonorrhea, but they may be complications of nonspecific infections. These abscesses develop when the urethral glands are infected and their ducts occluded. Periurethral abscesses are usually in the fossa navicularis where the glands are most numerous. They may rupture through the external surface and leave a permanent urinary fistula.

Reiter's Disease (Abacterial Urethritis).—Urethritis, conjunctivitis, and arthritis is a clinical triad known as Reiter's disease. The etiology of this disease is not known and tissue changes have not been investigated. Dunham, Rock, and Belt¹²³ have recovered a virus by inoculating embryonated eggs with filtered urethral and conjunctival exudates. They were able to produce conjunctivitis in mice intra-peritoneally inoculated with 48-hour allantoic cultures. Spontaneous recovery is the rule. In severe cases, there may be ulcerations on the buccal mucosa, skin on the plantar aspect of the feet, glans penis, urethra, and bladder. There may be acute iritis and keratitis.

Urethral Stricture.—Most of the urethral strictures are of inflammatory origin and the majority are complications of gonorrhreal urethritis. About 10 per cent are due to trauma, tuberculosis, syphilis, chancroid, periurethral abscess, caruncle, and granulomatous venereal lesions. In the female, obstetrical trauma is the chief cause of urethral stricture. Strictures due to gonorrhea do not produce symptoms until years later, whereas those caused by trauma or periurethral inflammation are well developed within a few weeks. Inflammatory strictures may occur in any portion of the urethra, but the vast majority are located in the bulbous and bulbomembranous portions which are the predominant sites of chronic

urethritis. The urethral wall is thick, indurated, and, at the site of the stricture, the wall is fibrous. The fibrosis involves the outer coats, corpus spongiosum, and Buck's fascia. There may be a thin band or a lengthy irregular mass of fibrous tissue.

Tumors of the Urethra.—The most common benign tumors of the urethra are caruncles, cysts, polyps, papillomas, adenomas, and angiomas. Fibromas and myomas are extremely rare.

Urethral caruncles are confined entirely to the female urethra. They represent regional or cir-



A.



B.



C.

Fig. 502.—*A*, Stricture of penile urethra; hypertrophy and large diverticulum of the bladder; *B*, squamous cell carcinoma of the glans penis; *C*, condyloma of the penis.

Urethrolithiasis.—Caleuli are rarely formed in the urethra. They are either dislodged bladder calculi or, when primary, they originate in a urethral diverticulum. Higgins and Hausfeld¹²⁶ reported a giant urethral calculus measuring 5 by 3 by 2.5 cm.

encircled prolapse of the urethra and are invariably secondarily infected due to trauma and irritation. Histologically, there are three somewhat arbitrary types. (1) The papillomatous type is frequently grossly lobulated as a result of clefts or crypts. The surface is covered by transitional

and stratified squamous epithelium in various places. The epithelium continues along the crypts from which sprouts extend deep into the stroma. Some of the epithelial lined crypts on cross section appear as deep-seated nests of epithelial cells. Such areas may be confused with carcinoma. The stroma is usually infiltrated with inflammatory cellular elements. (2) The telangiectatic caruncle is highly vascular. The vessels are so numerous that the lesion has the appearance of an angioma. Otherwise, the tumor frequently has a histological appearance similar to the papillomatous type. (3) The granulomatous type lacks the epithelial hyperplasia and is almost entirely composed of granulation tissue. There is an increasing opinion that the first two types of urethral caruncles represent precancerous lesions. Cases have been reported of carcinoma arising in a urethral caruncle.

Cysts of the urethra result from inflammatory occlusion of urethral glands. The cysts of the posterior urethra arise from occlusion of the periurethral and subcervical ducts. *Polyps* are usually encountered in the folds of the urethra. Some of the polyps are difficult to differentiate from fibromas and papillomas. *Papillomas* occur in any part of the urethra, but the majority are encountered about the vesicle neck at or near the meatus. They may be multiple and involve the entire urethra. The majority are sessile, wartlike, a few are pedunculated, and all are soft and of various shades of red. The papillomas are usually composed of squamous epithelial cells nourished by fibrovascular cores. Polyps and papillomas occur more frequently in the female urethra. *Adenomas* are small sessile or pedunculated tumors originating from the periurethral glands and usually encountered in the prostatic urethra. In the female, they arise from Skene's glands.

Squamous cell carcinoma of either male or female urethra is rare, but vulvo-urethral carcinoma is not infrequent. The favorite site in the male is in the cavernous and membranous portions. The tumors are associated with a high mortality, and the majority of the cases when first discovered have lymphatic invasion. *Adenocarcinoma* of the urethra is extremely rare. In the female, the tumor usually develops from Skene's glands. In the male, if the tumor arises in the posterior urethra, it is almost impossible to exclude prostatic origin. Carcinoma of the anterior urethra has a better prognosis than of the posterior urethra.

SCROTUM

Anomalies.—Arrest of development may result in the formation of a separate pouch for each testicle. Half of the scrotum corresponding to undescended testicle may be rudimentary. A cleft scrotum resembling labia majora is encountered in pseudohermaphroditism. Partial cleft scrotum may accompany other congenital defects of the genitourinary system.

Dermatological Lesions.—The common skin diseases of the scrotum are scabies (*Sarcoptes scabiei*), pediculosis, prurigo, eczema, erysipelas, psoriasis, and, not infrequently, syphilitic lesions.

Sebaceous cysts are not uncommon. They may be multiple. They develop slowly and occasionally become calcified.

Gangrene.—Gangrene of the scrotum may be caused by trauma or may be a complication of infectious diseases, phimosis, chancreoid, balantitis, and periurethritis. The idiopathic or spontaneous gangrene is unassociated with trauma or infection. The disease occurs at any age. It is more prevalent in middle or later years. Most of the cases resemble gas gangrene but *Clostridium welchii* is not always demonstrable. Various bacteria have been reported and those most frequently mentioned have been streptococci and *Cl. welchii*. A pitting edema rapidly develops; the skin color changes to dull pink, then greenish and finally becomes black. In some cases of *Cl. welchii* infection crepitation may be felt. Foci of necrosis appear simultaneously in isolated parts. These foci spread rapidly and coalesce to form a gangrenous mass. The gangrene may stop at the base of the penis or become widespread, extending to the anterior abdomen, or creeping, in rare instances, as far as the axillae. Sloughing usually occurs five to eight days after onset. The testicles remain unaffected and the tunica albuginea is found entirely intact. Death from toxemia may occur within seventy-two hours. The mortality is between 25 and 30 per cent. Microscopic examination reveals the usual findings of cellulitis followed by vascular changes, some hemorrhage, and finally necrosis.

Elephantiasis.—Elephantiasis of the scrotum is characterized by diffuse increase and fibrosis of the subcutaneous tissue and marked thickening of the skin, resulting in enlargement of the scrotum. The disease is the result of lymph stasis either from blocking of the lymphatics by microfilaria (*W. bancrofti*) or cicatricial closure of the lymph channels from chronic inflammation following trauma, excision of lymph nodes, or chronic lymphadenitis. In filariasis the adult worm obstructs the lymph channels. Secondary infection, according to some investigators, is necessary to produce elephantiasis. The live worm apparently provokes little or no inflammation. The dead and disintegrating forms stimulate proliferation of the intima followed by thrombosis and organization.

Hydrocele.—A hydrocele is an abnormal accumulation of serous fluid in the sac of the tunica vaginalis. Normally, there are a few drops of serous fluid between the visceral and parietal layers.

In the congenital type of hydrocele there is a direct communication with the abdominal cavity due to failure of closure of the funicular process. In infantile hydrocele there is accumulation of fluid in the partly closed funicular process and the sac of the tunica vaginalis, but there is no communication with the abdominal cavity. Acute hydrocele may be a complication of gonorrhea, tuberculosis, syphilis, erysipelas, rheumatism, typhoid, or neoplasms. Between 25 to 50 per cent of acute hydroceles are due to trauma.

The fluid of the hydrocele is odorless, viscid, and straw to amber colored. The usual amount varies from 4 to 10 ounces. It has a neutral reaction and its specific gravity varies from

1.020 to 1.026. It contains about 6 per cent protein (serum albumin, serum globulin, and fibrinogen), alkaline carbonates, and sodium chloride. Occasionally fibrous bodies coated with salts and fibrin are found floating in the fluid. The bodies originate from detached villous projections of the tunica vaginalis. If the hydrocele is infected, the fluid may be cloudy, or it may be brownish-red if slight hemorrhage has occurred. Microscopic examination of comparatively clear hydrocele fluid reveals a few mesothelial cells, lymphocytes, cholesterol crystals, lecithin bodies, and very often spermatozoa.

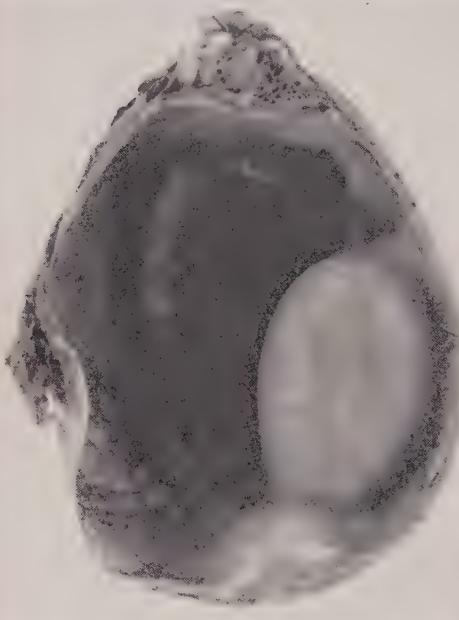


Fig. 503.—Hydrocele; normal testicle.

The sac of the hydrocele may be single or multiple chambered. The inner surface of the tunica vaginalis is usually smooth but there may be adhesions and fibrous projections. The wall is variously thickened, composed of scanty cellular fibrous tissue infiltrated with lymphocytes and some plasma cells. Calcific deposits are occasionally encountered.

Hematoma.—Hematoma of the scrotum is an effusion of blood within the tissues of the scrotal wall. The blood may collect beneath the dartos, between the tunica vaginalis and the fibrous coat (paravaginal hematoma), or in the scrotal septum. Hematomas are usually of traumatic origin, such as crushing, or a blow, or surgical trauma in operations on the scrotum or testicle. The writer has seen hematomas in acute leukemia and toxic purpura.

Hematocele.—Hemorrhage in the sac of the tunica vaginalis is known as hematocele. Spontaneous hematocele is slow and insidious in its development, whereas a rapidly develop-

ing hematocele is invariably due to trauma. The blood coagulates, fibrin settles out, organizes, and the wall becomes thick and rough. In long-standing hematocele the tunica vaginalis becomes enormously thickened with dense fibrous tissue which occasionally becomes partly calcified. Trauma may result in the formation of both hematoma and hematocele.

Tumors.—Ectopic tissue such as nodules of adrenal and splenic tissue have been found in the scrotum.

Lipomas of the scrotum usually arise from the cord. They occur between the ages of 40 and 60 and are seldom found in the adolescent or the aged. *Sebaceous* or *epidermoid* cysts are common. They are yellowish-white, firm, rounded, and range in size from a pinhead to 3 cm. in diameter. They occasionally become infected, and if infection persists for a long period they may become malignant. Small epidermoid cysts may become calcified. *Seborrheic keratosis*, verrucae, and condylomas are uncommon. *Angiomas* mainly occur in children.

The most common malignant neoplasm of the scrotum is the squamous cell carcinoma. Eti-



Fig. 504.—Organizing hematocele with compression and atrophy of the testicle; testicle incorporated in the left lateral wall. (Courtesy Dr. Joseph F. Kuzma.)

logically, the well-known and almost legendary "chimney-sweep's cancer" has been replaced by that arising among workers with tar, paraffin, and mineral oil, as well as the mule spinner of the cotton mill.

TESTES

Anomalies

Excluding malposition of the testicle, other anomalies are very rare. Anorchidism (congenital absence) and monorchidism (one testicle) have been reported. Synorchidism (fusion of testicles) occurs intra-abdominally. Polyorchidism has been found at operation and necropsy.

Ectopic Testis.—Ectopic testis is a congenital malposition of the testicle outside of the normal channel of descent. This ectopia, according to its location, is classified as interstitial, pubo-penile, femoral, crural, transverse, and perineal.

Cryptorchidism.—When the congenital malposition results in retention of the testicle anywhere along the route of descent, it is known as cryptorchidism. The cause of cryptorchidism is not always evident. The various apparent causes are short spermatic vessels or vas deferens, adhesions to peritoneum, poorly developed inguinal canal or superficial abdominal ring, maldevelopment of the scrotum or cremaster muscles, and hormonal influences. Incomplete descent is found quite frequently during the first few months of infancy. The incidence is about 4 per cent in boys under 15 years of age and about 0.2 per cent in adults. Histologically the cryptorchid testis before puberty does not differ from the normally descended organ. After puberty, the cryptorchid testicle is always smaller than normal. The capsule is somewhat thickened and wrinkled. The epididymis is separated from the mesorchium. The atrophic changes consist of complete absence or very little spermatogenesis, although spermatogenesis has occasionally been reported even in abdominal testis, and Rea¹³⁹ estimated that 10 per cent of untreated cryptorchids remain fertile. The basement membranes of the tubules thicken and hyalinize. The tubules may be lined with spermatogonia and spermatids, but in advanced atrophy the basement membranes are frequently lined only with Sertoli cells. Tubules with occluded lumina are not uncommon. The intertubular tissue is sparsely cellular, becomes more dense with age, and the interstitial cells of Leydig are conspicuous and vary in number. In some cases, the Leydig cells are decreased in number, in other cases they are increased both in size and in number. They are found single, in small groups, and occasionally in large masses. The writer has seen two cryptorchid testicles in which most of the atrophied organ was composed of large groups of polyhedral Leydig cells between which there was a scanty fibrous tissue and a few fibroed tubules. In rare instances, very few cellular elements are encountered and the entire testes becomes completely fibrosed. The cause of atrophy of undescended and ectopic testes is not known. There is convincing evidence that an optimum temperature is necessary for spermatogenesis, and that temperatures higher than that within the scrotum suppress spermatogen-

genesis. When aspermia or hypospermia exists, the testicle atrophies. The chief function of the scrotum is to regulate the temperature for the testes. Ischemia due to pressure, stressed by some authors, is definitely a minor factor in causing suppression of spermatogenesis in the cryptorchid.

Intersexuality.—A true hermaphrodite is one who possesses an ovary and a testicle or two ovotestes with external genitalia of both sexes. A pseudohermaphrodite possesses gonads of one sex and genitalia of either both or opposite sexes. In the male pseudohermaphrodite, testes are present but the internal genitalia are of both sexes, and the penis and scrotum are poorly developed. In the female pseudohermaphrodite, the ovaries are present usually in their normal position, the vagina is rudimentary and opens into the urethra, and the clitoris is hypertrophied.

Acquired Atrophy.—Excluding undescended testicles, acquired atrophy occurs in senility, prolonged hyperpyrexia, debility, avitaminosis, cirrhosis of the liver, hypothyroidism, schizophrenia, estrogen medication for carcinoma of the prostate, and diseases of the pituitary gland and hypothalamus. Faulty or suppressed spermatogenesis without other changes may questionably be considered as mild atrophy. The early findings in atrophy are degenerative changes of the spermatogonia cells. As atrophy progresses the germinative epithelial cells disappear, leaving only Sertoli cells resting on a thickened lamina propria. The seminiferous tubules become small, farther apart, and the interstitial cells of Leydig appear prominent. In some cases, the Leydig cells aggregate in large groups. Schwartz studied testicular biopsies from patients with carcinoma of the prostate treated with 360 to 1,700 mg. of stilbestrol. He found atrophy of the tubules, fibrous thickening of the basement membrane, arrest of spermatogenesis, and reduced number of Leydig cells.

Autolysis or complete disappearance of the testicle is very rare. Such condition may occur spontaneously or follow trauma. The rather striking finding is a cord containing the vas attached to the tunica albuginea which surrounds a small mass of fibrous tissue.

Thrombosis and Infarction.—Hemorrhage, thrombosis, and infarction of the testicle occur in trauma, torsion, leukemias, bacterial endocarditis, and periarteritis nodosa. Birth trauma may cause hemorrhage of the testicle. Many such hemorrhages are small hematomas which rapidly resorb.

Torsion.—A sudden twisting of the spermatic cord results in strangulation of the blood vessels serving the testicle and epididymis. The predisposing causes of torsion are free mobility and high attachment of the testicle. These anatomical features are found in such conditions as failure of the tunica vaginalis to close, large tunica vaginalis, absence of scrotal ligaments, gubernaculum testis or posterior mesorchium, or elongation of globus minor. Abnormal attachment of the common mesentery and vessels to the globus minor and lower pole of the testicle provide attachment of the testicle by a narrow stalk instead of by a wide

band. The exciting cause may be violent exercise or straining. The majority of the cases of torsion involve undescended testicles. Torsion may occur at any age. Cases have been reported in the newborn and in the very aged. The twist is commonly located in the free intra-vaginal portion of the cord. The twist may be a half turn to two full turns in either direction. The gross and microscopic findings depend on the degree of strangulation. Usually the picture is that of congestion and hemorrhage followed by necrosis of the testicle. The interstitial tissue may or may not be infiltrated with leukocytes. The tubules suffer varying degrees of degeneration and necrosis. At times, the entire testicle is found to be necrotic and acellular, and "ghost" tubules remain as conspicuous components in the histologic picture.

theria, typhoid fever, glanders, dengue fever, influenza, typhus fever, pneumonia, malaria, filariasis, and Mediterranean fever. Acute orchitis has also been encountered as a complication in focal infections such as sinusitis, osteomyelitis, cholecystitis, and appendicitis. A few cases have been reported associated with tonsillitis, acute articular rheumatism, and gout.

In bacteriemia, almost any organism may enter the testicle and produce acute orchitis or epididymo-orchitis. *Escherichia coli* and *Staphylococcus aureus* are the most common bacteria encountered, but *Neisseria gonorrhoeae*, streptococci, pneumococci, *Bacterium aerogenes*, *Bacillus pyocyaneus*, and Friedländer bacillus have been reported.

In acute orchitis the testicle becomes firm, tense, and swollen. In gonorrhreal orchitis,

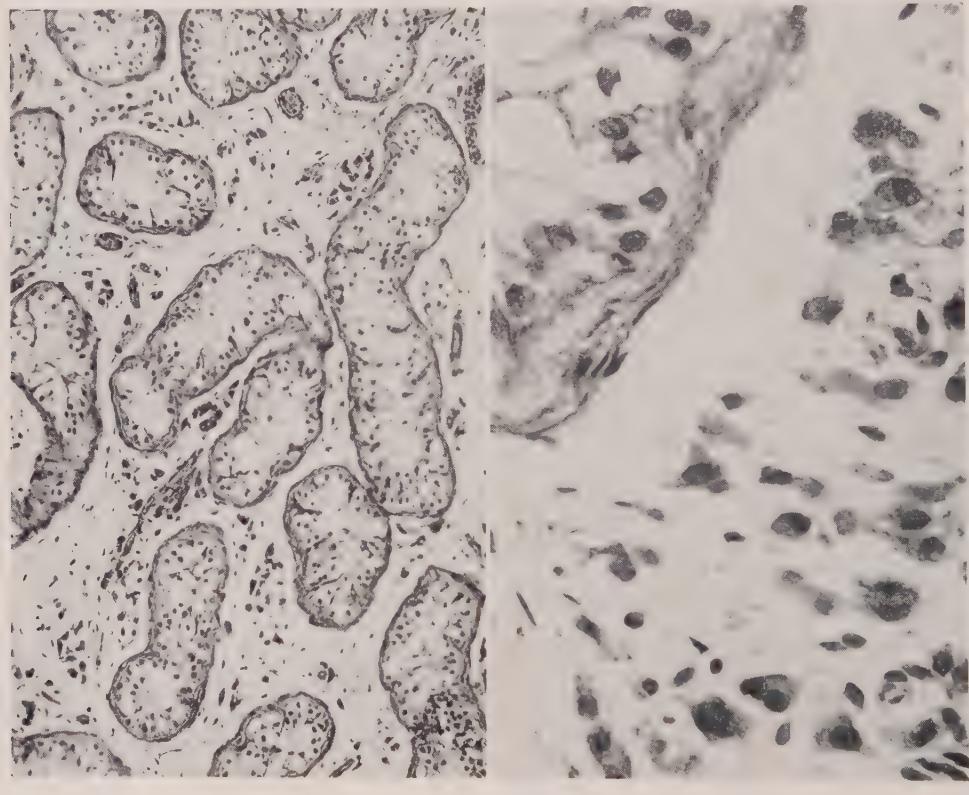


Fig. 505.—Atrophy of the testicle: A, thickened tubular basement membranes lined with degenerated spermatogonia and Sertoli cells; prominent Leydig cells in the interstitial tissue; B, aggregation of interstitial cells of Leydig; portion of a tubule lined with Sertoli cells.

Inflammation

Acute Orchitis.—Acute orchitis is either (1) an infection via the vas deferens and epididymis, (2) a combination epididymo-orchitis, or (3) a metastatic lymphogenous or hematogenous infection. Epididymo-orchitis is predominantly secondary to urethritis, cystitis, and seminal vesiculitis. Acute orchitis may be a complication of mumps, smallpox, scarlet fever, diph-

which is usually an extension from the epididymis, single or multiple abscesses develop, or the testicle may be diffusely infiltrated with neutrophilic leukocytes, lymphocytes, and plasma cells.

Chronic Orchitis.—Acute inflammation of the testicle may completely resolve, or the inflammation may continue in a chronic form. The inflammation may be focal or diffuse, unilateral or bilateral. Fibrosis may, in some cases, be seen grossly. There is a varying degree of de-

generation and disappearance of the tubular cells, and the walls of the tubules become thickened and hyalinized.

Orchitis of Mumps.—The incidence of orchitis as a complication of parotitis is between 20 to 30 per cent. This complication is rare in children. Grossly, the testicle is enlarged and the tunica albuginea contains punctate hemorrhages. The parenchyma in early stages appears edematous. Microscopically, the acute inflammatory process is characterized by diffuse interstitial infiltration with polymorphonuclear neutrophiles, lymphocytes, and histiocytes. Similar cellular elements fill the lumens and distend the tubules. Very few tubules suffer necrosis, but, in severe cases, the germinal epithelial cells and spermatogonia undergo degeneration with subsequent loss of spermatogenesis. In subacute and chronic phases of mumps orchitis, the interstitial tissue is infiltrated with lymphocytes. When degeneration has been extensive, the testicle becomes smaller and the thickened tubules are lined with a few Sertoli cells. The incidence of testicular atrophy and consequent sterility in this type of orchitis is not known.

Tuberculosis of the Testicle and Epididymis.—Tuberculosis of the testicle without involvement of the epididymis is rare. Discrete tubercles in the testicle may be encountered in generalized miliary tuberculosis. Tuberculosis of the epididymis is usually unilateral, may occur at any age, and is frequently associated with tuberculosis of the lungs and urogenital tract. The location of the primary focus of genital tuberculosis has stimulated considerable controversy among many investigators. Lowsley and Kerwin,¹⁴⁶ who stress the hematogenous route of infection, believe that the epididymis is the first of the genital organs to be affected. According to Barney¹⁴⁵ also, the primary focus in the majority of the cases is located in the epididymis. Young's¹⁴⁸ extensive surgical experience has convinced him that in most of the cases of genital tuberculosis, the primary site is found in the seminal vesicles. Walker¹⁴⁷ lends support to the advocates of the prostate gland or seminal vesicles as harboring the primary focus by pointing out the following interesting observations: (1) Tuberculosis of the epididymis is associated with tuberculosis of the prostate gland or seminal vesicles. (2) Tuberculosis of the prostate may exist without involvement of the epididymis. (3) Symptoms of prostatitis and vesiculitis often precede the appearance of tuberculous epididymitis. (4) When tuberculous prostatitis and epididymitis exist together, the tuberculous epididymitis appears in the lower pole of the epididymis which is the first station along the pathway of the invading organism. (5) Tuberculous nodules in the lower pole of the epididymis usually appear older than those of the upper pole.

The earliest lesions are seen as discrete or conglomeration, yellowish necrotic areas located in the globus minor. These microscopically reveal either characteristic tubercles or disorganized inflammatory cellular reaction consisting of polymorphonuclear leukocytes, plasma cells, desquamated epithelial cells, some large monocytes, occasional multinucleated giant

cells, and many acid-fast bacilli. The early lesion may regress and become calcified. Usually, however, there is progressive invasion until the entire epididymis becomes involved. When the tunica vaginalis is invaded, a considerable amount of serofibrinous or purulent exudate develops. Usually, the tunica vaginalis serves as a barrier against extension into the testicle and it is often surprising to find complete destruction of the epididymis and no invasion of the testicle. However, extensive invasion of the testicle does occur. The testicle may become adherent to the scrotum and the tuberculous process may penetrate the skin, producing tuberculous fistulas.

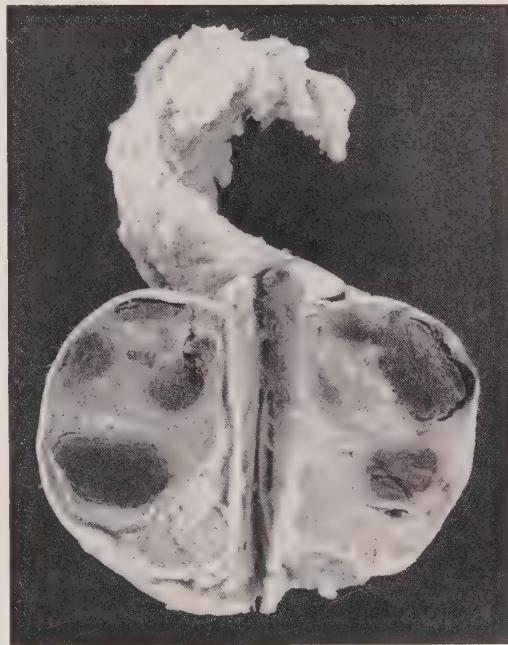


Fig. 506.—Testicle: Multiple infarcts in a case of periarteritis nodosa.

Syphilis.—The testicles in almost every syphilitic are involved. Warthin¹⁴⁹ demonstrated spirochetes in testicles without gross or histologic lesions, in both acquired and congenital syphilis. Chronic fibrous orchitis is frequently encountered in paresis. Herman and Klauder¹⁵⁰ found *Treponema pallidum* in the bone marrow and testicles before the development of chancre.

Syphilitic orchitis occurs either as a diffuse interstitial inflammation with fibrosis or as single or multiple gummas. Either of these types of lesions may be found in the acquired or congenital forms of syphilis. In contrast to tuberculosis, acquired syphilitic orchitis affects the testicle before the epididymis.

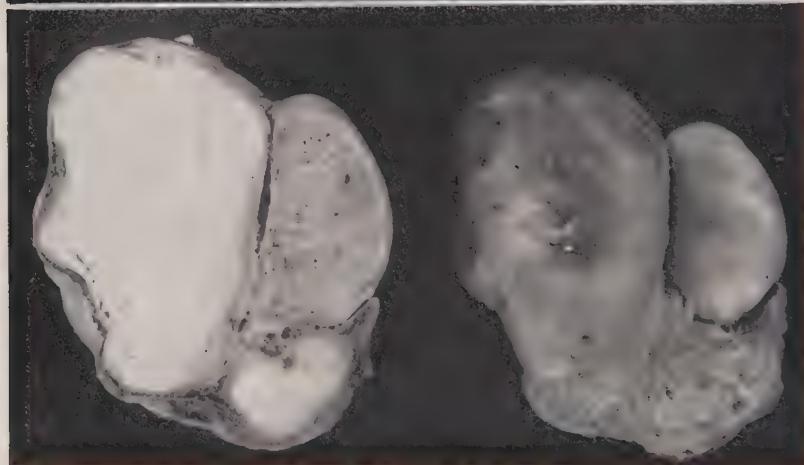
Grossly, the gummatous testicle is enlarged, firm, globular, smooth, and rarely nodular. When sectioned, the yellowish-white or grayish-white gummas bulge from the surrounding parenchyma. Extension of the gumma into the tunica vaginalis

causes adhesion to the scrotum, and secondary infection induces ulceration of the scrotum with herniation of the testicle. In fibrous syphilitic orchitis, the testicle is small and hard. When fibrosis is not pronounced, however, the testicle is of normal size and somewhat indurated.

Microscopically the gummas of the testicle are similar to those found elsewhere. The gumma

earlier granulation tissue is composed of lymphocytes, plasma cells, increase of interstitial connective tissue with many fibrocytes, and some multinucleated giant cells. There is decreased spermatogenesis and thickening of the basement membrane of the tubules. Spirochetes are readily demonstrable in this stage. In later stages there is diffuse fibrosis, peritubular and basal hyaliniza-

A.



B.

Fig. 507.—*A*, Tuberculosis of the epididymis; *B*, tuberculous epididymis about three times larger than the normal contiguous testicle.

is composed of a central area of caseation necrosis surrounded by a zone of edematous fibrous tissue infiltrated with plasma cells, lymphocytes, and occasional multinucleated giant cells. The syphilitic granulation tissue resembles that of tuberculosis except that it lacks the somewhat orderly zoned pattern of tuberculosis. The syphilitic granulation tissue is more diffuse, irregular, and contains more fibrous tissue. The

tion with necrosis of the tubular cells and shrinking of the tubules. The interstitial cells are usually well preserved and may often be hypertrophied. Spirochetes are seldom found in the fibrotic stage.

Chronic Proliferative Periorchitis.—Chronic proliferative (pseudofibromatous) periorchitis has frequently been designated as multiple fibromas of the tunica vaginalis. The etiology

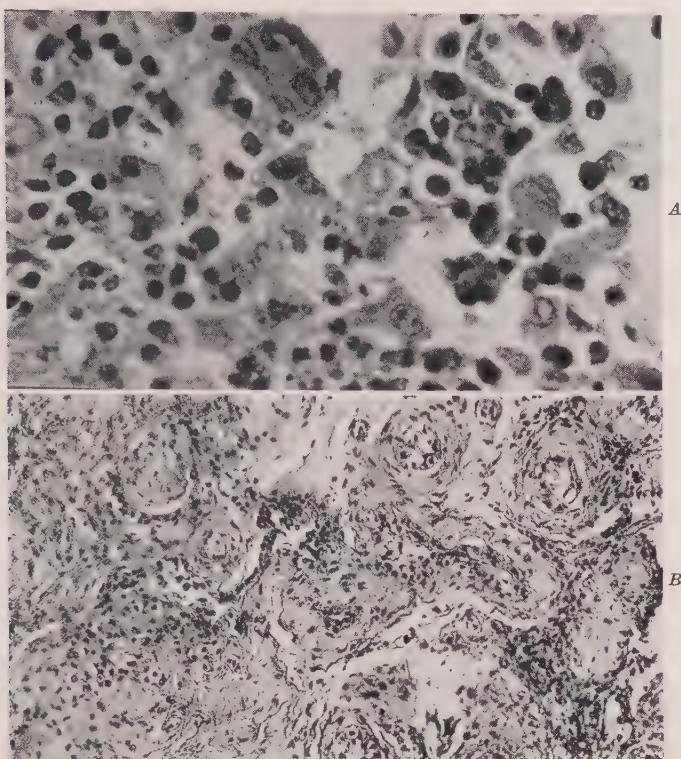


Fig. 508.—Syphilitic orchitis: *A*, granulomatous infiltration—lymphocytes, giant, plasma, and epithelioid cells; *B*, diffuse fibrosis.



Fig. 509.—Pseudofibromatous periorchitis. (Courtesy Dr. Robert S. Haukohl.)

of this peculiar inflammatory lesion is unknown. Some of the cases are definitely associated with trauma. The age incidence is between 20 and 40 years. Grossly, the tunica vaginalis is found to be markedly thickened and nodular. The surface is smooth and glistening. The nodules are multiple, scattered irregularly throughout the tunica vaginalis, and more numerous along the epididymis. The nodules range in size from 1 mm. to 2 cm. in diameter. On sectioning, some of the nodules are found to be circumscribed and resemble uterine fibroids, whereas others are ill-defined or confluent. Occasionally, some nodules become calcified. Microscopically, the sections reveal a scantily cellular collagenic fibrous tissue, often interlacing or having a whorling architecture, infiltrated with lymphocytes and plasma cells. In other cases there is very little inflammatory cellular reaction.

Tumors

BENIGN TUMORS

Benign tumors of the testicle proper are rare and the very few cases reported in the literature were angiomas, myomas, fibromas, myxomas, dermoids, and adenomatoid tumors. These tumors are more frequent in the epididymis. The most common benign tumors of the testicle are interstitial cell and adrenal rest tumors. The so-called "benign" adult teratoma is listed with the malignant (teratoid) tumors. The testicle harboring an *interstitial cell tumor* is usually enlarged. About 50 per cent are about two times larger than a normal testicle. The tumors are yellowish to brown and the consistency is that of adrenal cortical tissue. They are frequently lobulated and usually show no gross evidence of invasion. Microscopically, they are composed of polyhedral cells with one or two prominent nucleoli and abundant homogeneous or granular cytoplasm in which there may be vacuoles and occasionally refractile granules. The cells may be arranged in columns or nests separated by trabeculae of fibrous tissue. Interstitial cell tumors are difficult to differentiate from adrenal rest tumors. Patients with either tumor usually excrete an increased amount of 17-ketosteroids. Gynecomastia may be present in the adult, and all adolescent children with either interstitial cell or adrenal rest tumors have precocious physical and sexual development.

TERATOID TUMORS

The heterogeneous group of teratoid tumors occupies a unique place in the field of oncology. They were poorly understood until Friedman,¹⁵⁵ Moore,¹⁵⁶ and Dixon¹⁵⁷ properly elucidated their genesis.

About 4 per cent of the malignant neoplasms of the genitourinary system are teratoid tumors of the testicle. About 95 per cent occur between the ages of 20 to 45 years. The tumors are rarely encountered in individuals past 50 years. Although most of the reports emphasize that undescended testicles have a greater incidence of teratoid tumors, Carroll¹⁵³ has convincing evidence that malignancy in cryptorchidism is rare. By comparing the incidence of tumors in undescended to descended testes, Campbell¹⁵⁴ has shown that the incidence of malignancy in ectopic testes is four times greater. By far, the great majority of the tumors of ectopic testes are seminomas.

The parent cell of teratoid tumors is the germ cell and the variety of teratoid tumors that differentiate from it is revealed in Fig. 511.

The principal types of teratoid tumors are: (1) seminoma, (2) embryonal carcinoma, (3) immature teratoma (teratocarcinoma), (4) mature (adult) teratoma, and (5) choriocarcinoma.

Seminoma.—Compared with the incidence of other teratoid tumors, seminoma is the most frequent, occurs in the older age group, and is relatively less malignant. Undescended testicles harbor this tumor more frequently than other forms of teratoid tumors. The involved testicle may be only slightly enlarged or may be ten times larger than normal, yet it usually maintains almost its normal contour. This gross feature is due to the fact that the tunica covering is seldom invaded. The neoplasm is opaque grayish-white or yellowish-white and not uncommonly contains yellowish and yellowish-brown areas of necrosis. Some tumors are homogeneous whereas others are distinctly lobulated. The large tumors replace the entire testicle whereas the small tumors are circumscribed but not encapsulated. Hemorrhagic necrosis is rare and cysts are never found in pure seminomas.

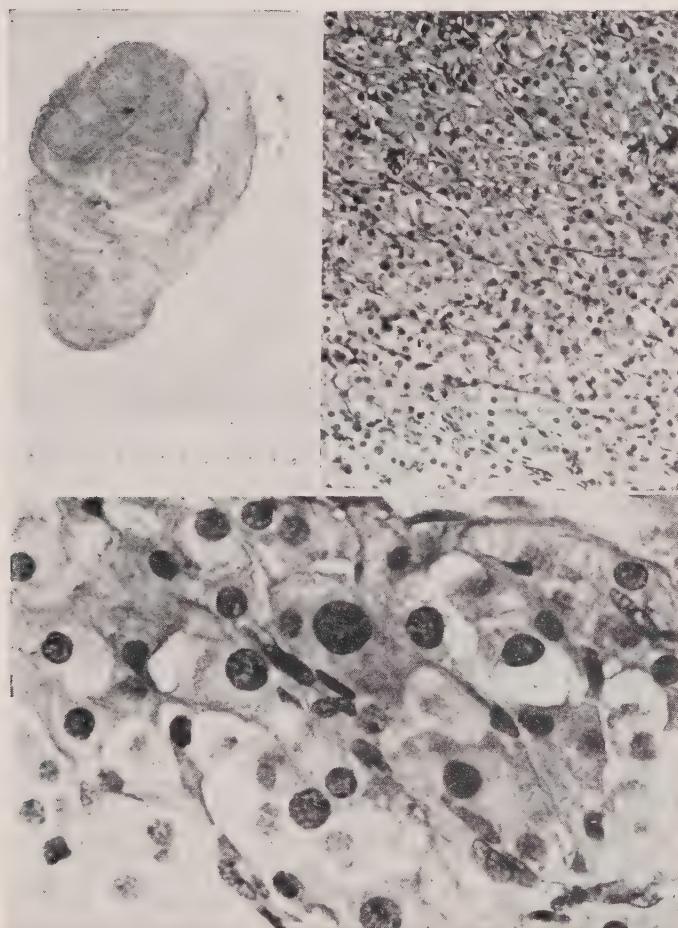


Fig. 510.—Interstitial cell tumor of the testicle from a 7-year-old boy with hypergenitalism. (From Anderson, Synopsis of Pathology, The C. V. Mosby Co.)

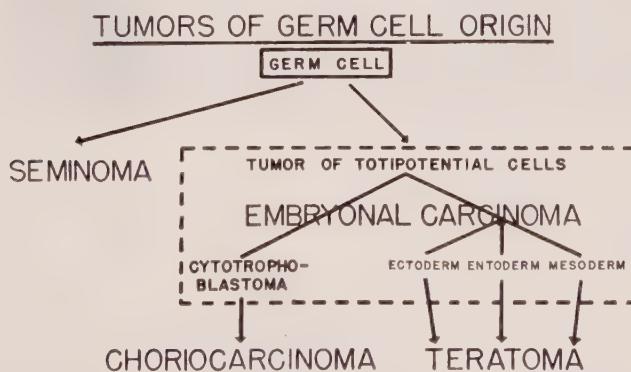


Fig. 511.—Histogenesis of teratoid tumors of the testicle. (Courtesy Dr. F. J. Dixon.)

Microscopically, seminomas are readily recognized because of their monocellularity. The cells are moderately large, round, cuboidal or polyhedral, quite uniform in size, and the majority reveal distinct cell borders. The cytoplasm is usually quite clear but occasionally it is slightly stained. The relatively large, round, centrally located nucleus may occupy one-third to one-half of the cell space. The nucleolus is prominent, slightly eosinophilic, and some nuclei have two nucleoli. The nuclear chromatin net

Lymphocytic infiltration (*lymphoid stroma*) in seminomas, designated by some authors as a subvariety, has no prognostic value. Variant forms of seminomas contain areas of cellular pleomorphism with cells resembling trophoblasts. In some cases the seminoma cells are difficult to differentiate from embryonal carcinoma cells. Occasionally, both types of cells are seen in the same tumor, and in such instances the morphologic character in the different cell masses is quite obvious.



Fig. 512.—Seminoma of the testicle infiltrating the spermatic cord.

is quite characteristic, being uniformly distributed and beaded at the interstices. Irregular cell masses are separated by delicate fibrous tissue septa which may be the only supporting stroma that divides the tumor into lobules. However, in some tumors the stroma may be quite fibrous, granulomatous, or lymphocytic. Not uncommonly, the cells are arranged in cords or have a tubular pattern.

Embryonal Carcinoma.—Although a better term for embryonal carcinoma would be welcome, the structural variability of this tumor precludes a change. The tumor is usually bulky, rapidly growing, and invasive. The tissue is soft, gray, often necrotic, and hemorrhagic, but rarely cystic. Microscopically, there is considerable architectural and cellular variation. Some embryonal carcinomas

are monocellular sheets, others are papillary and glandular. The few monocellular forms are difficult to differentiate from seminomas. The distinguishing features are larger cells, greater cellular anaplasia, nuclear pleomorphism, and absence of trabecular supporting stroma. The nuclear chromatin is coarsely clumped in embryonal cells whereas in the seminoma cells the nuclei are clearer and chromatin particles are finer with beaded interstices of the chromatin net. The epithelial cells of the glandular and papillary forms are cuboidal or columnar and not as anaplastic as the embryonal cells of the solid monocellular type. Friedman and Moore,¹⁵⁵ and Dixon and Moore¹⁵⁷ have conclusively shown that by somatic and trophoblastic differentiation of totipotential cells of embryonal carcinomas, teratomas and choriocarcinomas develop. One may therefore encounter immature somatic and trophoblastic elements in embryonal carcinomas.

Choriocarcinoma.—Choriocarcinomas are the most malignant of the teratoid tumors. They are usually small, red, soft, sometimes cystic, and always hemorrhagic and necrotic. Some choriocarcinomas are almost entirely necrotic and many blocks of tissue must be examined before viable cells are found. The writer has seen a case in which the entire testicular tumor was necrotic and intact cells were found only in the metastasis. Microscopically, two types of cells, the cytотrophoblasts and syncytiotrophoblasts, and the villuslike structures render this tumor highly characteristic. The cytотrophoblasts are polyhedral cells having a clear or pinkish cytoplasm with relatively large hyperchromatic nuclei. They lie in sheets or make up the major portion of the villuslike structure which are usually bordered by syncytiotrophoblasts. The syncytiotrophoblasts are large, irregular, often huge, bizarre cells with pseudopodia extending between other cells. Their cell wall is indistinct. They possess a large amount of azurophilic cytoplasm which is frequently vacuolated. Their deeply staining nuclei are large, irregular, and pyknotic. Some of the cells are multinucleated. Syncytial cells suffer degenerative changes more readily than the cytотrophoblasts.

Immature Teratoma (Teratocarcinoma).—The immature teratoma is composed of a variety of differentiated somatic structures (see mature teratoma) mingled with malignant cell masses recognized as embryonal carcinoma, seminoma, choriocarcinoma, and occasionally sarcoma elements. Any one, any two, or all of these malignant structures associated with a variety of adult cellular components may be present in a single tumor. Grossly, these tumors are quite large, solid, or have a mixture of solid and cystic areas.



Fig. 513.—Immature teratoma (teratocarcinoma) of the testicle infiltrating the spermatic cord.

Mature (Adult) Teratoma.—The designation of "benign" to mature teratomas should be discarded. Clinical experience and serial histologic studies have demonstrated that many adult teratomas proved to be malignant. The tumors are of moderate size, grayish-white, and cystic. They are well circumscribed and fre-

quently a definite capsule separates the tumor from the testicular tissue. The cysts may contain sebaceous or mucoid material. Histologically, no two teratomas appear alike. Various somatic structures are present. These consist of cutaneous (sebaceous glands, hair follicles, sweat glands), respiratory, enteric, neurogenic, muscle, and cartilaginous structures lying between mesenchymal tissue.

Excluding seminomas, the areas of metastasis produced by other teratoid tumors may vary in structure. Friedman and Moore¹⁵⁵ emphasized that adult teratomas are matured teratocarcinomas and that when metastasis is associated with an adult teratoma, the totipotential cells had metastasized before the primary teratoid tumor had completely differentiated. They further believe that a metastatic focus of totipotential (embryonal) cells may differentiate into various mature somatic structures. Therefore, the metastasis of an embryonal carcinoma may be entirely composed of embryonal cells or trophoblastic cells or a



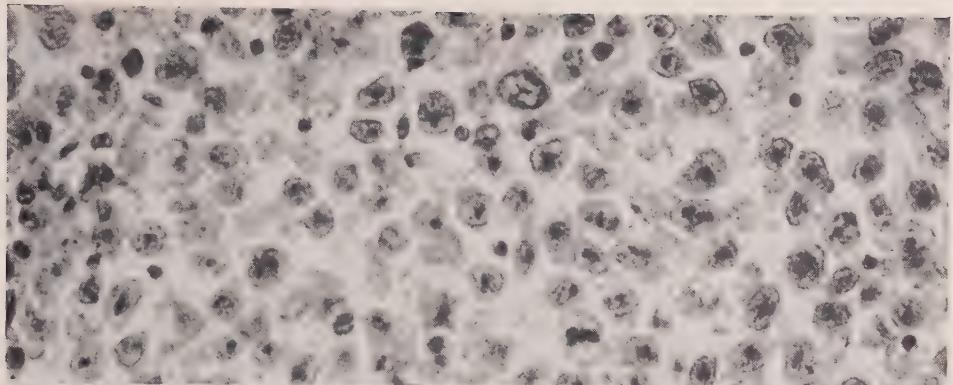
Fig. 514.—Mature (adult) teratoma of the testicle.

Metastasis.—Metastasis of teratoid tumors is mainly lymphogenous. They involve the retroperitoneal lymphatics and extend along the spine to the mediastinum. They may also metastasize to the lungs and liver. Seminomas metastasize later than other teratoid tumors. Embryonal carcinoma has a high incidence of metastasis and a marked mortality rate. The incidence of metastasis of immature teratoma is slightly higher than that of adult teratoma but the prognosis is poor for both of these tumors. Metastasis of choriocarcinoma is most extensive.

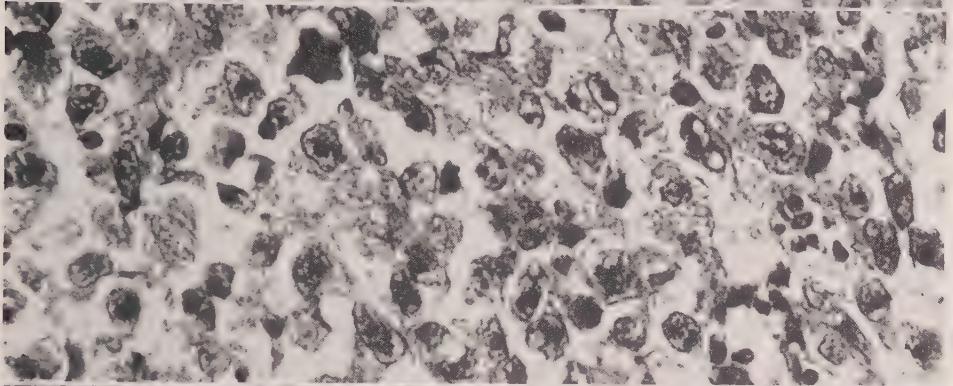
mixture of these cells with somatic elements, but rarely will the metastasis be entirely of seminoma cells. As a rule, the metastasis in a given case is uniform, but occasionally the structure of metastatic foci varies. Thus, in one site of metastasis, there may be embryonal carcinoma whereas in another site, there may be a mixture of cell elements.

Hormonal Aspect of Teratoid Tumors.—The blood and urine of some patients with teratoid tumors of the testicle contains choriogonadotropic hormone similar to that of pregnant women, and when injected in suitable animals, yields a positive pregnancy test. In addition, there may be a large amount of follicle-stimulating hormone. By assaying a 24-hour specimen of urine and determining the number of units, Ferguson and others claimed

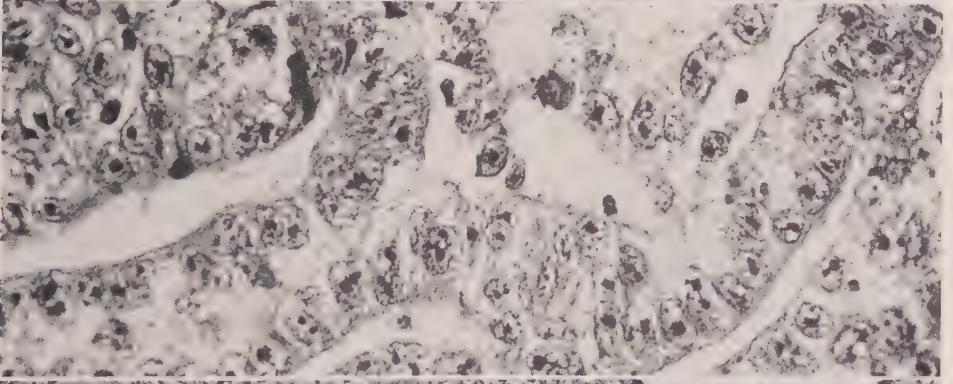
A.



B.



C.



D.

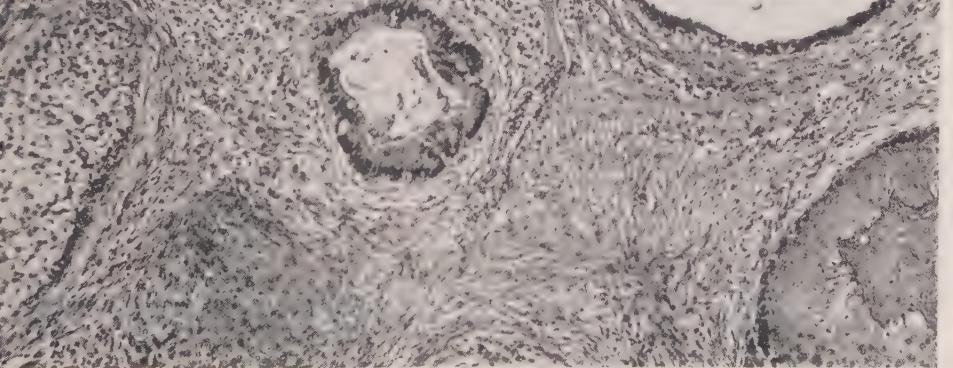


Fig. 515.—Teratoid tumors of the testicle. *A*, Seminoma. *B*, Monocellular embryonal carcinoma. *C*, Embryonal adenocarcinoma. *D*, Mature teratoma showing from left to right, cartilage, bronchial epithelium, part of a cyst, partly keratinized squamous cell nests and intervening mesenchymal tissue.

they could predict the histologic type of teratoid tumor. Most investigators have failed to verify this observation. Biologic tests for gonadotropic hormones should be performed in every case where an enlarged testicle is suspected of harboring a teratoid tumor. The test is also useful postoperatively where a positive result indicates metastasis. Negative results after radiation therapy do not always indicate a good response to treatment.

Spermatogenesis and Spermatozoa

Spermatogenesis is dependent on a great variety of conditions. Excluding the various diseases of the genital system, abnormal or deficient spermatogenesis occurs in deficiencies of vitamins A and E, malnutrition, endocrine disturbances, debility, and environmental states causing fatigue, nervousness, and anxiety. Decrease or cessation of spermatogenesis may occur after a loss of 25 to 35 per cent of body weight.

Semen analysis has become an important laboratory procedure in problems of sterility. The important examinations include appearance, viscosity, cell count, motility, and morphology. The volume of an ejaculated specimen does not seem important since the average for barren and sterile marriages is about 3 cubic milliliters. In Hotchkiss,¹⁵⁹ analysis of 200 fertile men, the volume ranged between 0.6 to 9 cubic centimeters. Normal semen is grayish-white, opalescent, of mucoid character, having tapioca-like bodies that liquefy in a few minutes, whereas abnormal semen is more translucent or may contain blood. Increased viscosity hampers motility and shortens the life of the sperm. Increased viscosity is usually due to disease of the prostate and seminal vesicles. Body heat promotes motility and shortens longevity. At room temperature, spermatozoa may remain motile for twenty-four hours. Specimens that lose their motility within six hours at room temperature are considered abnormal. The likelihood of conception is dependent on the abundance of sperm. The normal cell range is from 150 to 2,000 million per cubic centimeter. Counts below 60 million occur in barren marriages. When semen used for artificial insemination contained less than 100 million per cubic centimeter, pregnancy did not develop. The morphologic study of the spermatozoa is important. The space allotted does not permit a lengthy description of the various morphologic characteristics of abnormal sperm. The most important pathologic shapes that occur in sterile men are (1) tapering cells, with tapered caudal end of head; (2) duplicate cells, with double heads, double nuclei, or double tails; (3) giant head cells; (4) pinhead cells; and, (5) amorphous cells, with heads of various shapes.

Tumors of Epididymis

The epididymis should not be considered as a separate body. It is part of the testicle and, therefore, usually a partner with the testicle to the major diseases described in the preceding paragraphs. However, primary tumors may arise in the epididymis. Longo, McDonald, and Thompson¹⁶² collected 134 primary tumors of

the epididymis from the world literature. The ages ranged from 21 to 78 years and the average was about 41 years. Tumors occurred four times more often in the globus minor than in the globus major, and the left side was affected twice as often as the right. The tumors ranged from 1 to 5 cm. in diameter.

The most common tumor of the epididymis is the *adenomatoid tumor*. This tumor has been reported under a variety of headings such as mesothelioma, lymphangioma, adenomyoma, etc. Similar tumors are encountered in the tunica vaginalis, spermatic cord, posterior aspect of the uterus, fallopian tube, and ovary, indicating that such tumors develop along the course of the mesonephric duct. They are of epithelial origin and the term adenomatoid tumor is appropriate. The tumors are discrete, non-tender, firm, rounded or ovoid nodules averaging 2 to 3 cm. in diameter. They are circumscribed and the majority are encapsulated. They are composed of glandlike structures in a loose or dense fibrous tissue stroma mixed with smooth muscle fibers. The glandlike structures are lined with flat, cuboidal, or low columnar cells. Many of the cells are vacuolated. Some of the cells may be arranged in cords. Most of the tumors contain aggregates of lymphocytes.

Leiomyoma is the second most common tumor of the epididymis and is frequently accompanied by a hydrocele. Other benign tumors reported in the literature are *angiomas*, *fibromas*, *lipomas*, *adrenal rests*, and *cholesteatomas*. The reported teratoid tumors and dermoid cysts were probably associated with teratoid tumors of the testicle.

Carcinomas and sarcomas are extremely rare.

Spermatic Cord

Anomalies of the spermatic cord consist of congenital absence or congenital atresia of the vas deferens. Sterility is present when these conditions are bilateral. Complete or incomplete duplication of the vas deferens has been reported.

Inflammation of the vas deferens is known as *vasitis* or *deferentitis*, whereas inflammation of the entire spermatic cord is termed *funiculitis*. Lymphangitis, phlebitis, and thrombo-angiitis may be due to a variety of causes. *Vasitis* may be due to extension of epididymitis or lymphogenous transportation from urethritis and cystitis. The etiology of some cases of both *vasitis* and *funiculitis* is not definitely known and in these cases trauma and focal and general infections are suspected. Tuberculosis of the spermatic cord is secondary to tuberculous epididymitis and seminal vesiculitis. Filarial *funiculitis* is associated with elephantiasis of the penis and scrotum. There is lymphangiectasia and fibrosis of the interstitial tissue. The walls of the lymph vessels become thickened and frequently reveal obliterative lymphangitis with calcific and crystalline deposits. Calcified filariae may be found in whorls of hyalinized fibrous tissue. The various inflammatory cells encountered in filarial *funiculitis* are lymphocytes, plasma cells, eosinophiles, and, in some cases, multinucleated giant cells.

Torsion of the spermatic cord is described on page 631.

Varicocele is a common condition in which the veins of the pampiniform plexus are dilated, elongated, and their tortuosity increased. The cause of primary or idiopathic varicocele is not definitely known. Secondary or symptomatic varicocele is due to pressure on the spermatic veins or its tributaries by enlarged liver and spleen, marked hydronephrosis, muscular strain, and abdominal tumors. Primary varicocele usually involves the left spermatic cord and is predominant in young boys.

Tumors.—Various tumors involving the spermatic cords are recorded in literature. Benign tumors are lipomas, fibromas, myomas, angiomas, cystadenomas, teratomas, and dermoid cysts. Sarcomas and carcinomas are rare. Lipoma is the most common tumor involving the spermatic cord.

Seminal Vesicle

Seminal vesiculitis may be nonspecific, gonorrhoeal, or tuberculous. Any pathogenic bacteria may cause seminal vesiculitis. The structure of this sacculated body with its diverticula and mucosal folds and poor drainage favors chronicity whenever infection sets in. Therefore, as a focus of infection, like that of the prostate, seminal vesiculitis should not be overlooked. Infection may reach the vesicles by extension from the posterior urethra, from above through the genital tract, and by the blood stream from distant foci. Seminal vesiculitis frequently accompanies any type of urogenital infection. The seminal vesicles are almost always involved in tuberculosis of the genital tract. *Abscess* of the vesicles is usually unilateral and may follow any type of genital infection. The abscess may rupture into the perirectal tissue and occasionally penetrate the bladder or rectum. *Stricture* of the ducts is sometimes a complication of transurethral prostatic resection. Obstruction of the ejaculatory ducts favors development of *calculi* which usually are found in men past 40 years. *Calcification* may be focal or diffuse. It is readily recognized in roentgenograms. Most of the cases are associated with genital tuberculosis. In the aged, calcification occurs as a peculiar metamorphosis of the muscularis with no evidence of inflammation. *Neoplasms* of the seminal vesicles are rare. The majority of the tumors are simple cysts. The benign solid and cystic tumors reported in literature are myomas, fibromyomas, and cystadenomas. Carcinomas and sarcomas are very rare.

References

Ureter

1. Lowsley, O. S.: J. Urol. **48**: 611, 1942 (anomalies).
2. Nourse, M. H., and Moody, N. C.: J. Urol. **56**: 525, 1946 (postcaval).
3. Campbell, F. W.: J. Urol. **60**: 31, 1948 (megaloureter).
4. Irvin, G. E., and Krause, J. E.: Arch. Path. **45**: 752, 1948 (megaloureter and hydroureter).
5. Pessin, S. B.: Urol. & Cutan. Rev. **43**: 752, 1939 (cysts).

Calculi

6. Dourmashkin, R. L.: J. Urol. **54**: 245, 1945.
7. Goldman, N.: J. Urol. **28**: 371, 1932.

8. Marangos, G., and Porter, G. E.: Brit. J. Surg. **32**: 524, 1945.
9. Higgins, C. C., and Warden, J. G.: Ann. Surg. **127**: 257, 1948.

Diverticula

10. Campbell, M. F.: Am. J. Surg. **34**: 385, 1936.
11. Dodson, A. I.: J. Urol. **52**: 526, 1944.
12. Culp, O. S.: J. Urol. **58**: 309, 1947.

Obstruction

13. Deming, C. L.: J. Urol. **50**: 420, 1943.
14. McKay, R. W.: Am. J. Surg. **11**: 67, 1931.
15. Pugh, W. S.: Internat. J. Med. & Surg. **47**: 355, 1934.

Tumors

16. Foord, A. G., and Ferrier, P. A.: J. A. M. A. **112**: 596, 1939.
17. Hundley, J. M., and Hunter, J. S.: J. Urol. **58**: 176, 1947.
18. Kraus, J. E.: Urol. & Cutan. Rev. **48**: 522, 1948.
19. Vest, S. A.: J. Urol. **53**: 97, 1945.

Urinary Bladder

Extrophy

20. Wyburn, G. M.: J. Anat. **71**: 201, 1937.
21. Higgins, C. C.: J. Urol. **63**: 852, 1950.

Cystitis

22. Cristol, D. S., and Greene, L. F.: Surgery **18**: 343, 1945 (gangrenous).
23. Tenenbaum, G., and Saifer, S.: Am. J. Surg. **38**: 378, 1937 (necrosis).
24. von Brunn, A.: Arch. f. mikr. Anat. **41**: 294, 1893 (cell nests).
25. Hoyt, H. S.: J. Urol. **59**: 424, 1948 (cystitis cystica).
26. Cristol, D. C., and Broders, A. C.: J. Urol. **55**: 260, 1946 (malakoplakia).
27. Sterling, W. C.: J. A. M. A. **112**: 1326, 1939 (follicular).
28. Saver, H. R., and Blick, M. S.: J. Urol. **60**: 446, 1948 (cystitis glandularis).
29. Ortmayer, M.: J. Urol. **60**: 757, 1948 (cystitis emphysematosa).
30. Seaman, J. A.: J. Urol. **63**: 105, 1950 (interstitial).
31. Ultzmann, H.: Wien. klin. Wochenschr. **60**: 467, 1948 (phlegmonous).
32. Finestone, E. D.: Surg., Gynec. & Obst. **62**: 93, 1936 (syphilis).
33. Ormond, J. K., and Hemming, J. G.: J. Urol. **52**: 23, 1944 (gumma).
34. Saver, H. R., and Metzner, W. R. T.: J. Urol. **59**: 38, 1948 (monilia).
35. Hatch, W. E., and Wells, A. H.: J. Urol. **52**: 149, 1944 (actinomycosis).
36. Rohn, J. G., Davila, J. C., and Gibson, T. E.: J. Urol. **63**: 660, 1951 (coccidiomycosis).
37. Newman, H. R.: J. Urol. **50**: 440, 1943 (bilharziasis).
38. Glen, J. E., and Bailey, R. S.: J. Urol. **66**: 294, 1951 (trichomonial).
39. Musiani, U.: J. d'urol. med. et chir. **53**: 3, 1946 (irradiation).
40. Crance, A. M.: J. Urol. **56**: 588, 1946 (grain mite infestation).

Diverticula, Herniation, and Spontaneous Rupture

41. Burns, E.: Ann. Surg. **119**: 1944 (diverticula).
42. Boun, H. K.: Urol. & Cutan. Rev. **40**: 484, 1936 (herniation).
43. Feigal, Wm., and Polzak, J. A.: J. Urol. **56**: 196, 1946 (spontaneous rupture).
44. Nansom, E. M.: Australia & New Zealand J. Surg. **20**: 215, 1951 (stenosis).

Calculi and Foreign Bodies

45. Cristol, D. S., and Greene, L. F.: S. Clin. North America **25**: 987, 1945 (calculi).
46. Lepreau, J., and Jenkins, R. H.: New England J. Med. **229**: 937, 1943 (calculus—1,134 grams).
47. Muller, M., and Macquet, P.: Ann. de med. leg. **18**: 447, 1938 (foreign bodies).
48. Tudor, R. B.: Am. J. Dis Child. **65**: 591, 1943 (foreign bodies in children).

Neurogenic Dysfunction

49. Thompson, G. J.: U. S. Nav. M. Bull. **45**: 207, 1945.

Amyloidosis

50. Senger, F. L., Thomley, M. N., and McManus, R. G.: *J. Urol.* **63**: 790, 1950.
51. Roen, P. R., and Wiener, J.: *J. Urol.* **66**: 119, 1951.

Tumors

52. Evans, E. E.: *J. Urol.* **38**: 212, 1937 (aniline dye).
53. Kretschmer, H. L.: *Surg., Gynec. & Obst.* **47**: 145, 1928 (leukoplakia).
54. Schmitz, H. E.: *Urol. & Cutan. Rev.* **52**: 124, 1948 (endometriosis).
55. Hueper, W.: *Arch. Path.* **25**: 856, 1938 (aniline tumors).
56. Kerwin, T. J.: *J. Urol.* **49**: 1, 1943 (virus etiology).
57. Goyanna, R., Emmett, J. L., and McDonald, J. R.: *J. Urol.* **65**: 391, 1951 (extrophy and carcinoma).
58. Higgins, C. C.: *Ann. Surg.* **93**: 886, 1931 (benign tumors).
59. Kleitsch, W. B.: *J. Urol.* **65**: 60, 1951 (leiomyoma).
60. Friedman, N. B., and Kuhlenbeck, N.: *J. Urol.* **64**: 657, 1950 (adenomatoid).
61. Segal, A. D., and Fink, H.: *J. Urol.* **47**: 453, 1942 (hemangioma).
62. Hamm, F. C.: *J. Urol.* **44**: 227, 1940 (cystadenoma).
63. Wyman, H. E., and Chappell, B. S.: *J. Urol.* **63**: 526, 1950 (ganglioneuroma).
64. Ravich, A., Stout, A. P., and Ravich, R. A.: *Ann. Surg.* **121**: 361, 1945 (myoblastoma).
65. Davis, T. A.: *Northwest Med.* **48**: 182, 1949 (hamartoma).
66. Deming, C. L.: *J. Urol.* **63**: 815, 1950 (papilloma).
67. Ash, J. E.: *J. Urol.* **44**: 135, 1940 (epithelial tumors).
68. Copridge, W., Roberts, L. C., and Culp, D. A.: *J. Urol.* **65**: 540, 1951 (adenocarcinoma).
69. Boylan, R. N., Greene, L. F., and McDonald, J. R.: *J. Urol.* **65**: 104, 1951 (in diverticula).
70. Fister, G. M., and Lund, A. J.: *J. Urol.* **65**: 401, 1951 (myosarcomas).
71. Burros, H. M., Drapiewski, J. F., and Purcell, J. B.: *J. Urol.* **63**: 122, 1950 (lymphosarcoma).
72. Bugbee, H. G., and Dargeon, H. W.: *J. Pediat.* **19**: 656, 1941 (sarcoma).
73. Crane, A. R., and Tremblay, R. G.: *Ann. Surg.* **118**: 887, 1943 (osteogenic sarcoma).
74. Jewett, H. J., and Strong, G. H.: *J. Urol.* **55**: 366, 1946 (metastasis).
75. Kleiman, A. H.: *J. Urol.* **56**: 644, 1946 (implants).
76. Harrison, J. H., Botsford, T. W., and Tucker, M. R.: *Surg., Gynec. & Obst.* **92**: 129, 1951 (cytologic diagnosis).

Urachus

77. Cherry, J. W.: *J. Urol.* **63**: 693, 1950 (patent).
78. Brodie, N.: *Ann. Surg.* **69**: 243, 1945 (cysts).
79. Hurwitz, S. P., Jacobson, E. B., and Ottenstein, H. H.: *J. Urol.* **65**: 87, 1951 (carcinoma).

Prostate

80. Lloyd, F. A., and Bonnett, D.: *J. Urol.* **64**: 777, 1950 (cysts).
81. Davies, J. A.: *Canad. M. A. J.* **54**: 268, 1946 (echinococcus cysts).
82. Gentile, A. J.: *J. Urol.* **57**: 746, 1947 (calculi).
83. Moore, R. A.: *Arch. Path.* **22**: 24, 1936 (thrombosis).
84. Rogers, W. G.: *J. Urol.* **57**: 484, 1947 (infarcts).
85. Hock, E.: *J. Urol.* **56**: 353, 1946 (diverticula).
86. Cooper, H. G., and MacLean, J. T.: *Canad. M. A. J.* **54**: 136, 1946 (bacteria).
87. Baker, W. J., and Graf, E. C.: *J. Urol.* **66**: 254, 1951 (tuberculosis).
88. Lowsley, O. S.: *Clinical Urology*, Baltimore, 1944, Williams & Wilkins Co., Vol. I (hyperplasia).
89. Huggins, C.: *Bull. New York Acad. Med.* **28**: 696, 1947 (hyperplasia).

90. Deming, C. L.: *Surg., Gynec. & Obst.* **50**: 588, 1940 (hyperplasia).
91. MacLoed, D.: *Brit. J. Urol.* **77**: 85, 1945 (hyperplasia).
92. Moore, R. A.: *J. Urol.* **50**: 680, 1943 (hyperplasia).
93. Ockerblad, N. F.: *J. Urol.* **56**: 81, 1946 (hyperplasia).
94. Simonds, L.: *Path. Anat. v. L. Aschoff* (ed. 2) **2**: 408, 1923 (hyperplasia).
95. Baron, E., and Angrist, A.: *Arch. Path.* **32**: 787, 1941 (carcinoma).
96. Boyer, W. F.: *J. Urol.* **63**: 334, 1950 (carcinoma—cytology).
97. Rezek, P. R., Coplan, M. M., Woods, F. M., and Melvin, P. D.: *J. Urol.* **66**: 379, 1951 (estrogen therapy).
98. Sutton, E. B., and McDonald, J. R.: *Am. J. Clin. Path.* **18**: 607, 1943 (metaplasia).
99. Woodard, H. Q., and Dean, A. L.: *J. Urol.* **57**: 158, 1947 (acid phosphatase).
100. Leander, W. R., and Wheelock, M. C.: *J. Urol.* **63**: 162, 1950 (leiomyosarcoma).
101. Hunt, R. W.: *New York State M. J.* **43**: 513, 1943 (rhabdomyosarcoma).
102. Kirshbaum, J. D., Larkin, H. S., and Culver, H. C.: *J. Urol.* **50**: 597, 1943 (lymphosarcoma).
103. Kaufman, J. J., and Berneike, R. R.: *J. Urol.* **65**: 297, 1951 (leiomyoma).
104. Albers, D. A., McDonald, J. R., and Thompson, G. J.: *J. A. M. A.* **139**: 299, 1949 (carcinoma cells).
105. Graves, R. C., Warren, S., and Harris, P. N.: *Tr. Am. A. Genito-Urin. Surgeons* **29**: 179, 1936 (lymphogenous metastasis).
106. Batson, O. V.: *Ann. Surg.* **112**: 138, 1940 (hematogenous metastasis).
107. King, L. S., and Cox, T. R.: *Am. J. Path.* **27**: 801, 1951 (sarcoma).
108. Peters, N., and Young, J. D.: *J. A. M. A.* **145**: 556, 1951 (cytologic diagnosis).
109. Peters, N., and Benjamin, J. A.: *Surg., Gynec. & Obst.* **91**: 660, 1950.

Penis

110. Smith, E. B., and Custer, R. P.: *J. Urol.* **63**: 546, 1950 (lymphogranuloma venereum).
111. Getzoff, D. L.: *J. Urol.* **56**: 243, 1946 (fusospirochetosis).
112. Scott, W. W., and Scardino, P. L.: *South. M. J.* **41**: 173, 1948 (Peyronie's disease).
113. McCrea, L. E.: *J. Urol.* **60**: 776, 1948 (erythroplasia).
114. Wilson, J. F.: *J. Roy. Army M. Corps* **68**: 22, 1937 (condylooma).
115. Andrews, E. W.: Cited by Barney: *Ann. Surg.* **46**: 890, 1907 (carcinoma).
116. Ngai, S. K.: *Am. J. Cancer* **19**: 259, 1933 (carcinoma).
117. Lenowitz, N., and Graham, A. P.: *J. Urol.* **56**: 458, 1946 (carcinoma).
118. Smith, E. B., and Custer, R. P.: *J. Urol.* **63**: 546, 1950 (adenocarcinoma).
119. Levant, B.: *J. Urol.* **52**: 63, 1944 (sarcoma).

Urethra

120. Pate, V. A., and Bunts, R. C.: *J. Urol.* **65**: 108, 1951 (diverticula).
121. Copelli, M., and Gennari, A.: *Boll. d. Soc. med. di Parma* **8**: 7, 1915 (gonococcemia).
122. Baier, G. F.: *Bull. U. S. Army M. Dept.* **9**: 679, 1949 (nonspecific urethritis).
123. Dunham, J., Rock, J., and Belt, E.: *J. Urol.* **58**: 212, 1947 (Reiter's disease).
124. Brannan, D.: *J. Urol.* **66**: 242, 1951 (stricture, female).
125. Beard, D. E., and Goodyear, W. E.: *J. Urol.* **59**: 619, 1948 (stricture, male).
126. Higgins, C. C., and Hausfeld, K. F.: *Cleveland Clin. Quart.* **15**: 9, 1948 (urethrolithiasis).
127. Lazarus, J. A.: *Urol. & Cutan. Rev.* **37**: 604, 1933 (benign tumors).
128. Palmer, J. K., Emmett, J. L., and McDonald, J. R.: *Surg., Gynec. & Obst.* **87**: 611, 1948 (caruncle).
129. Zaslow, J., and Priestley, J. T.: *J. Urol.* **58**: 207, 1947 (carcinoma, male).
130. Brack, C. B., and Farber, G. J.: *J. Urol.* **64**: 710, 1950 (carcinoma, female).

131. Moffett, J. D., and Banks, R.: J. A. M. A. **146**: 1288, 1951 (prolapse).

Scrotum

132. Morley, N. V., and Best, J. W.: J. Urol. **58**: 458, 1947 (calcified cysts).
 133. Mair, G. B.: Lancet **1**: 464, 1945 (gangrene).
 134. Bell, L. N.: Surg., Gynec. & Obst. **29**: 199, 1919 (elephantiasis).
 135. Olken, H. G.: Am. J. Path. **21**: 81, 1945 (splenic tissue).
 136. Southam, A. H., and Linell, E. A.: Brit. J. Surg. **11**: 223, 1923 (tumors).

Testes

137. Cecil, A. B.: J. Urol. **58**: 384, 1947 (ectopic).
 138. Lewis, L. G.: J. Urol. **60**: 345, 1948 (cryptorchidism).
 139. Rea, C. E.: Arch. Surg. **44**: 27, 1942 (cryptorchidism).
 140. Nelson, W. O., and Heller, C. G.: J. Clin. Endocrinol. **5**: 13, 1945 (atrophy).
 141. Schwartz, M.: Proc. Am. Fed. Clin. Research **2**: 97, 1945 (atrophy-stilbestrol).
 142. Ravich, R. A.: J. Urol. **57**: 875, 1947 (infarction).
 143. Foley, W. J.: Am. J. Surg. **70**: 105, 1945 (torsion).
 144. Charney, C. W., and Meranze, D. R.: J. Urol. **60**: 140, 1948 (mumps orchitis).
 145. Barney, J. B.: Am. J. Urol. **7**: 497, 1911 (tuberculosis).
 146. Lowlesley, O. S., and Kerwin, T. J.: Clinical Urology, Baltimore, 1944, Williams & Wilkins Co. (tuberculosis).
 147. Walker, K. M.: Lancet **1**: 435, 1913 (tuberculosis).
 148. Young, H. H.: Arch. Surg. **4**: 334, 1922 (tuberculosis).
 149. Warthin, A. S.: Am. J. M. Sc. **152**: 508, 1918 (syphilis).
 150. Herman, L., and Klauder, J. V.: Am. J. M. Sc. **159**: 705, 1920 (syphilis).
 151. Goodwin, W. E.: J. Urol. **56**: 438, 1946 (fibrous periorchitis).
 152. James, D. C., and Shupe, R. D.: J. Urol. **63**: 718, 1950 (interstitial cell tumors).
 153. Carroll, W. A.: J. Urol. **61**: 396, 1949 (tumors in cryptorchid).

154. Campbell, H. E.: Arch. Surg. **44**: 353, 1942 (tumors in cryptorchid).
 155. Friedman, N. B., and Moore, R. A.: Mil. Surgeon **99**: 573, 1943 (teratoid tumors).
 156. Moore, R. A.: J. Urol. **65**: 693, 1951 (teratoid tumors).
 157. Dixon, F. J., and Moore, R. A.: Personal communication.
 158. Twombly, G. H.: J. A. M. A. **118**: 106, 1942 (hormone excretion).

Spermatogenesis and Spermatozoa

159. Hotchkiss, R. S.: Fertility in Men, Philadelphia, 1944, J. B. Lippincott Co.
 160. Mack, W. S.: Glasgow M. J. **25**: 87, 1945.
 161. Gersh, I.: J. Urol. **66**: 450, 1951.

Epididymis

162. Longo, V. J., McDonald, J. R., and Thompson, G. I.: J. A. M. A. **147**: 937, 1951 (neoplasms).
 163. Condhere, J. T., and Flynn, J. E.: J. Urol. **56**: 448, 1946 (adenomatoid tumors).

Spermatic Cord

164. Nelson, R. E.: J. Urol. **63**: 176, 1950 (congenital absence).
 165. Wiensky, A. O., and Samuels, S. S.: Ann. Surg. **78**: 785, 1923 (inflammation).
 166. Coley, B. L., and Benjamin, L.: Am. J. Surg. **76**: 15, 1948 (filaria).
 167. Warwick, W. T.: Lancet **1**: 517, 1931 (varicocele).
 168. Beneventi, F. A.: Am. J. Surg. **71**: 783, 1946 (varicocele).
 169. Thompson, G. J.: Surg., Gynec. & Obst. **62**: 712, 1936 (tumors).

Seminal Vesicles

170. Herlin, H. C.: J. A. M. A. **143**: 880, 1950 (inflammation).
 171. Shea, J. D., and Rogers, J. W.: J. Urol. **58**: 132, 1947 (calcification).
 172. Gee, E. M.: Brit. J. Urol. **20**: 72, 1948 (tumors).

Chapter 23

THE LUNG

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STRUCTURE AND FUNCTION

The structure of the lungs is such as to allow the greatest possible interchange of gases through the walls of the capillaries, consistent with the safety of the organism. From the functional standpoint the structure is analogous to a highly vascular areolar tissue into which are thrust innumerable fine tubes through which the tissue is aerated. Abundant elastic tissue is provided in parenchyma, bronchi, and pleura to aid in expressing the expended air. The thoracic cage and respiratory muscles furnish the mechanism for alternate expansion and compression of the elastic structure for continuous exchange of gases. Protection of the delicate, blood-filled structure not only from trauma but also from excessive drying is provided by its interior location and by the passage of air through a long, finely subdivided series of tubes, lined by moist epithelial membranes. Partial protection against the accumulation and damaging effects of finely divided particulate matter, floating as dust in the air, is furnished by a film of seromucinous secretion and by ciliary action.

The details of structure of the respiratory tree and parenchyma can be obtained from textbooks of anatomy and histology and from the detailed studies of C. C. Macklin,¹ W. S. Miller,² C. G. Loosli,³ and others. This outline is intended merely to emphasize certain structural peculiarities which have a bearing upon the facts and theories of the pathogenesis of diseases peculiar to the respiratory system. One of the most obvious peculiarities of the respiratory tract in man, subjecting him to a disadvantage not shared by most other animals, is its almost vertical position. It is not sufficiently appreciated that the relative positions of the mouth, larynx, and trachea, plus the effect of gravity, have a decisive importance in the pathogenesis of many diseases, particularly those which depend upon the introduction of foreign bodies, bacilli-laden secretions, or exudates into the bronchial tree, whence the liquid substances may be drawn into the parenchyma by respiratory movements. Of secondary importance is the difference in the angle of the two primary bronchi and the location of the carina to the left of the middle at the lower end of the trachea. The fact that the right bronchus is more nearly vertical and in direct continuation with the trachea determines the greater frequency with which foreign bodies or liquids drop into the right bronchus than into the left. It seems probable also that fine droplets and dust, suspended in inspired air, will be

less frequently interrupted by contact with bronchial mucosa when the angles of the serially branching bronchi are less acute. The more frequent involvement of the right lung by bacterial infections is attributable to this difference in angle of the two primary bronchi.

All of the lining of trachea and bronchi and of the larynx except the vocal cords is covered by columnar epithelium, provided with numerous mucus-secreting goblet cells and cilia whose wavelike motion tends to sweep mucus and entrapped dust or other particulate matter upward to the vestibule of the larynx where it lodges until voluntarily expelled and expectorated or swallowed.

Under ordinary circumstances, the epiglottis efficiently prevents solid or liquid substances in the mouth, nose, and pharynx from dropping into the larynx. Its nervous control is relaxed or abolished during sleep, general anesthesia, alcoholic intoxication, and other comatose states, and it is during such a state that the aspiration of foreign substances usually occurs. When the protective action of the epiglottis is removed, the only protection provided is that of position, so that gravity will assist in evacuating the trachea and bronchi. The effects of ciliary action obviously will be of no effect in clearing the bronchi of liquid exudates, saliva, blood, or vomitus when the quantity is sufficiently large to flow rapidly over the mucous surfaces. In the anesthetized experimental animal it can easily be demonstrated that the flow of even a minute quantity of liquid is determined by the position of the trachea and bronchi and the force of gravity. Nonirritating liquids such as iodized poppy-seed oil (Lipiodol) can be introduced at will into any part of the bronchial tree by simply placing the subject in the appropriate position. From the bronchi, even moderately viscid liquids such as mucoserous secretions, vegetable or mineral oils, will be drawn into the parenchyma of the lung, from which they cannot escape except by dilution and absorption or by the action of phagocytes.

The successive divisions of the bronchial tree are bronchi of three orders, bronchioles of several orders down to the terminal bronchioles, and respiratory bronchioles which begin with a diameter of about 0.5 mm. The bronchioles lose their cartilage when they reach a diameter of about 1.0 mm. The cilia are continued down to the first part of the respiratory bronchiole, where they are lost and the columnar epithelium becomes low cuboidal. The respiratory bronchiole takes its name from the fact that there are lateral outpouchings of alveoli in its wall before it subdivides into several alveolar ducts,

from which, in turn, arise numerous alveolar sacs and alveoli. Besides cartilage, the walls of the bronchi and bronchioles contain elastic and collagenous fibers, smooth muscle, and mucous and mucoserous glands, located usually under the muscular layer. The glands extend as far peripherally as the cartilage, but goblet cells can be found in the terminal bronchioles. Smooth muscle envelops the walls of bronchioles in the form of interlacing strands so that their contraction results in shortening as well as constriction of the lumen. Some muscle fibers extend out to the end of the respiratory bronchioles and, to a certain extent, into the walls of the alveolar ducts.

The alveolar sacs and alveoli are thin-walled structures, opening by relatively wide apertures into the alveolar ducts and respiratory bronchioles. Their walls consist of dense nets of anastomosing capillaries, supported by abundant interlacing reticulum fibers, and their openings are surrounded by wavy bundles of collagenous fibers. Elastic fibers are present in the inter-alveolar septa. The interstices of the capillary nets contain numerous histiocytes, which, in the resting state, lie close against the surfaces of capillaries. When stimulated, these "septal cells" become actively motile and phagocytic, frequently relinquishing their attachment to the alveolar walls and becoming free "dust cells" or "alveolar macrophages" in the air spaces. Careful studies of tissue cultures and numerous *in vivo* experiments have demonstrated that the nucleated alveolar "epithelium" of the earlier histologists was none other than the highly phagocytic cells of the macrophagic system. The "nonnucleated epithelial plates" were artifacts produced by crude silver impregnation methods and, according to Loosli,³ represent the outlines of the endothelial cells of capillaries. If a continuous epithelial membrane existed, it certainly would constitute a serious barrier to the exchange of gases. True epithelium forms an interrupted lining for the respiratory bronchioles and, in the presence of chronic inflammation, may proliferate to form a lining for deformed alveolar ducts and sacs in much the same way that bronchial epithelium sometimes extends into the lumen of an old abscess cavity. The normal alveolus is not an impervious sac, analogous to the acinus of a secretory gland, but a sievelike structure with many openings (Kohn's pores) through which any watery fluid, such as edema fluid, may flow freely into contiguous air sacs. These openings are most often demonstrated in fibrinous pneumonia, in which bundles of filaments of fibrin can be seen, passing through them from one air sac to another. They are readily demonstrable in the normal lung by experimental methods.⁴

Lymphatic tissue, nodular and diffuse, is fairly abundant in the mucosa of the bronchi and in the connective tissue around bronchial cartilage, especially at the bifurcations of bronchi and bronchioles, generally diminishing as the tubes become smaller. The alveolar sacs and alveoli contain neither lymphocytes nor lymph channels, but lymphatic capillaries have been demonstrated in the walls of the alveolar ducts. These drain toward the hilum along

the courses of bronchioles, bronchi, and blood vessels. Collections of lymphocytes are inconspicuous in the adventitia of the blood vessels of the normal lung but usually increase in number and form nodules in a lung which has been the site of repeated acute inflammatory processes or of prolonged irritation. The lymph channels of the parenchyma are said to have no valves⁵ except in the narrow zone under the pleura. In this zone the flow of lymph is directed toward the pleural surface, joining the dense network of channels in the pleura from which the lymph is collected in larger ducts and flows along the pleura to the hilar nodes. Ultimately all of the lymph from the right lung reaches the right lymphatic duct and that of the left lung is collected by the thoracic duct. The direction of flow from parenchyma and pleura is always toward the hilum.

DISTURBANCES OF CIRCULATION AND VASCULAR DISEASE

Congestion and Edema.—Chronic valvular disease of the heart and myocardial insufficiency mainly are responsible for long-standing pulmonary congestion. This type of abnormality of circulation leads to deficient oxygenation of blood in the lesser circulation and to slowly progressive anatomical changes in the lungs which vary with the duration of the disturbance and its severity. Overdistention of the alveolar capillaries and stasis of blood combine to increase the permeability of the endothelial tubes. The fluid which escapes into the alveolar spaces is reabsorbed in large part and the extravasated erythrocytes are phagocytized and broken down by alveolar macrophages. Perivascular and peribronchial lymph spaces as well as the veins and capillaries are dilated. Perivascular, peribronchial, and interlobular connective tissues are thickened as a result of edema and increased numbers of cells. Fibrosis occurs as a late sequel, affecting the lung diffusely but particularly the peritruncal tissues. The fibrosis, with the brownish discoloration due to hematogenous pigmentation, is responsible for the consistency and color of "brown induration" of the lungs. The fully developed pathologic picture is most commonly associated with the mitral stenosis and insufficiency of chronic rheumatic disease of the heart. In late decompensation, edema usually develops in the dependent portions of the lungs and constitutes a serious danger in that bacteria implanted in the protein-rich fluid

often lead to a rapidly fatal "hypostatic" or "terminal" pneumonia.

Chronic hyperemia of the tracheobronchial mucosa is followed by mucosal thickening and hypersecretion of mucus. Persistent irritative cough with expectoration of thick turbid mucus may be the result of congestion alone and is not necessarily complicated by infection. Large macrophages, loaded with blood pigment, are so constantly present in the mucus and so characteristic of the disease that they are often referred to as "heart failure cells."

in its greater content of proteins and greater specific gravity, but, for the pathologist, its association with the other elements of exudative inflammation, especially fibrin and leukocytes, constitutes the most reliable means of differentiation.

Thrombosis, Embolism, and Infarction.

—**Primary thrombosis** of the larger pulmonary vessels is uncommon, but thrombosis of the small veins of the lungs within areas involved by acute inflammation is exceedingly common. The importance of the latter, however, is comparatively

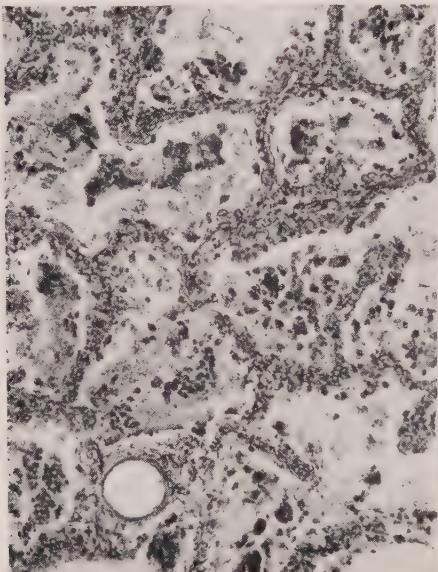


Fig. 516.

Fig. 516.—Chronic congestion of the lung in a case of rheumatic heart disease with mitral insufficiency. The alveolar walls are thickened. Alveolar spaces contain pigment-laden macrophages and precipitated protein.

Fig. 517.—Pulmonary edema. Vacuoles of entrapped air in some of the alveoli.

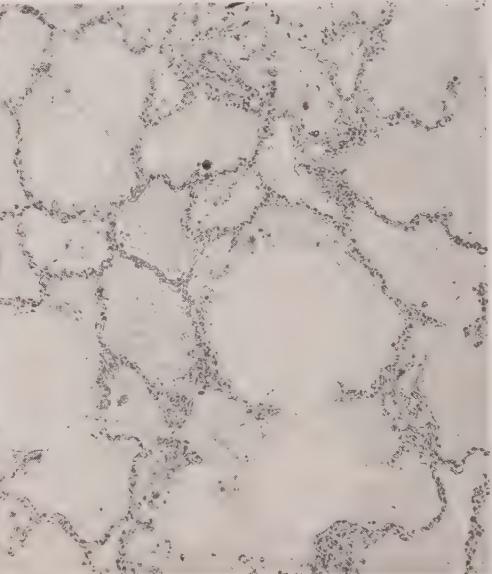


Fig. 517.

Acute hyperemia of the lungs is a fundamental part of the local reaction to injury and therefore a part of acute inflammation due to bacterial infection or to irritation by noxious gases, liquids, or soluble dusts. It consists of dilatation of capillaries in the involved area, with the passage of a greater than normal quantity of fluid into the alveolar spaces.

If the rate of extravasation of fluid with its proteins and electrolytes is greater than that of reabsorption by blood and lymph, edema results. The fluid of acute inflammation differs from that of a noninflammatory transudate

minor. Such thrombi sometimes become loosened from their moorings and lead to embolization through the major arterial circulation, with infarction of kidneys, spleen, and brain. The parietal thrombi which are occasionally formed within the trunk and principal rami of the pulmonary artery probably arise from infection of the arterial wall with local damage to the intima. Direct extension along the wall from thrombotic endocarditis of the pulmonary valve is observed in occasional cases. Thrombosis on the basis of ulcerated atheromata, so common in the aorta, rarely occurs in the pulmonary arteries.

Pulmonary embolism is very common. All masses which are liberated from thrombi in the systemic veins are arrested in the pulmonary arterial tree except those so minute that they can pass through pulmonary capillaries. If the lumen of a large artery becomes obstructed, infarction frequently results (Figs. 518 and 519). In the case of obstruction of the smaller branches, collateral circulation from adjoining trunks of pulmonary and bronchial arteries is usually adequate to prevent infarction, due to the free anastomoses through the capillary network which both arterial systems supply.

15 to 30 cm. in length usually has had its origin in the femoral and external iliac veins, while a thicker mass with multiple tree-like branches can arise only in the bed of the internal iliac vein, most commonly originating in the uterine veins. Either type may be built up in the successively larger veins until the thrombotic mass reaches the lumen of the inferior vena cava. If a large part of such a thrombus becomes loosened at once, it is arrested at the bifurcation of the pulmonary artery, completely obstructing the main stem or extending into both rami as a "straddling embolus." Failure of



Fig. 518.



Fig. 519.

Fig. 518.—"Straddling" embolus at bifurcation of artery. Hemorrhagic infarct of upper lobe. The middle and lower lobes are collapsed as a result of obstruction of the major bronchi by aspirated mucus.

Fig. 519.—Hemorrhagic infarct of lower lobe. At the hilum of the lower lobe, the arterial lumen is filled with adherent clot, following embolism.

Sudden complete occlusion of the stem or of either of the primary rami of the pulmonary artery commonly leads to death from circulatory failure. The usual sources of such large emboli are the external or internal iliac veins and their larger tributaries. A cylindrical clot from

pulmonary circulation is practically complete and death occurs in a few minutes. With the exception of dilatation of the right side of the heart, no pathologic changes which are the result of the arterial obstruction will be recognizable. Survival for an hour or more is usual follow-

ing obstruction of one pulmonary ramus or some of its principal branches, after which some degree of edema of the affected lung will be found.

If arteries of the second or third order are obstructed, infarction may occur but death usually does not occur as a direct result of the embolization unless a major portion of the arterial tree is occluded. Experimentally, infarction does not occur unless passive congestion is present in the area involved,⁶ and it is common experience that infarcts are found most often in lungs already the seat of chronic congestion from cardiac insufficiency. Occasionally, small infarcts are found in otherwise apparently normal lungs, particularly in the sharp angles of the ventral and diaphragmatic margins where collateral circulation is not so free, due to the presence of pleura on two sides of the angle.

In their early stages, pulmonary infarcts are dark red, firm, and moist. On the pleural surface which forms the base of the mass, there is a delicate film of fibrinous exudate, and the surface of the infarct appears blue or purple through the slightly edematous serous membrane. A fresh infarct usually is not sharply defined but merges with surrounding parenchyma in an irregular zone of edema and fading hemorrhage. After a week or more, the color changes to red-brown and then pale tan or gray as the blood is gradually broken down and removed from the site. Organization begins in a week or ten days, progressing from the periphery toward the center of the infarct. Necrosis is not always complete in the smaller lesions and in some instances the organized residue retains some semblance of alveolar structure but shows thickened septal walls and various degrees of obliteration of the air spaces (Fig. 541). These residues resemble localized areas of organized pneumonia but disclose their nature by the presence of an organized embolus-thrombus in the lumen of the artery which supplies the area.

FAT AND BONE MARROW EMBOLISM.—Fat embolism is not a cause of infarction of the lung because of the small size of the globules which are filtered out in pulmonary capillaries and arterioles. Patchy hyperemia and edema constitute the only changes recognizable in the lung itself except the stuffing of numerous small blood vessels with oil or fat, which is demonstrable only by appropriate staining of microscopic sections.

Since massive fat embolism is commonly associated with traumatic injuries involving fractures of bones or extensive crushing of soft parts, thrombo-emboli and even recognizable masses of bone marrow⁷ may be found in the pulmonary arteries and arterioles. When death occurs it is not often attributable to the effects of fat embolism of the lungs alone but rather to the embolization of arterioles which supply the vital centers of the brain and to the general circulatory deficiency associated with shock (see p. 131).

AMNIOTIC FLUID EMBOLISM.—In 1941 Steiner and Lushbaughs called attention to a clinical-pathological entity of rapidly developing shock and unexpected death occurring in women during or soon after parturition. Foreign particles of vernix caseosa, including epithelial squames, lanugo hair, and in some cases the mucus and epithelial cells of meconium, were found to occlude many of the small arteries, arterioles, and capillaries of the lungs. Similar particulate matter of the amniotic fluid was found in the venous channels of the uterus. In some cases, the only other significant alterations were pulmonary congestion and edema and dilatation of the chambers of the right side of the heart. Gross and Benz⁸ were able to demonstrate embolic material in blood withdrawn at autopsy from the inferior vena cava and pulmonary artery of a woman who had died in obstetric shock and recommended the examination of blood from the right ventricle in cases where necropsies were not obtainable. Other confirmatory observations have been accumulating in the medical literature but the frequency of occurrence of this entity is not yet established.

TUMOR EMBOLISM.—Other body cells and tissues may occasionally gain access to the venous circulation and give rise to pulmonary embolism. Masses of tumor cells which have invaded systemic veins are swept into the blood stream and become impacted in the rami of the pulmonary arteries. Such masses often degenerate, become incorporated in secondarily formed thrombi, and are organized *in situ*; or, if they remain viable, they may penetrate the vascular walls, continue to grow and produce metastases. Rarely the tumor emboli may be massive (e.g., malignant hepatoma, renal carcinoma) obstructing the major branches of pulmonary arteries.

Masses of chorionic syncytial cells and single cells resembling those of the chorionic epithelium are frequently found in the pulmonary vascular channels of women who have died during pregnancy or soon after parturition. These have no pathological significance since they are incapable of progressive growth and do not obstruct any significant portion of the pulmonary vascular bed. They should not be mistaken for metastatic chorionepithelioma. (See also pages 1092 and 1096.)

Pulmonary Arteriosclerosis.—Mild degrees of sclerosis of the pulmonary artery and its branches are practically always present after middle age. Under 40 years of age, such changes are somewhat more common in association with those conditions of the heart and lungs which increase pressure in the pulmonary circulation, i.e., mitral and aortic stenosis, chronic pulmonary emphysema, and chronic inflammatory diseases of the lungs leading to fibrosis. After 40, the

degree of pulmonary sclerosis is not significantly greater in the presence of such conditions than in their absence.¹⁰ The only difference between the lesions occurring in pulmonary arteries and those occurring in the systemic arteries is that they are much milder in the former. Ulcerated atheromata of the pulmonary vessels are rare. The common mild lesions have little functional importance. Only in the most advanced degree of sclerosis of the small arteries is there presumptive evidence of pulmonary hypertension in the form of hypertrophy of the right ventricle.

The term "primary pulmonary sclerosis" has been applied to those cases of sclerosis of the pulmonary vessels in which none of the common conditions thought to favor pulmonary hypertension is present. Since 1909 pulmonary arteriosclerosis has been associated in the clinical and pathologic literature with the name of Ayerza, a Buenos Aires physician who in 1901 described a case of heart failure with extreme cyanosis but did not mention the state of the pulmonary blood vessels. "Ayerza's disease" has come to mean many different things to different writers. To some it is any case of cardiac failure associated with pulmonary arteriosclerosis. To others it means primary pulmonary sclerosis, and to still others it is a clinical syndrome characterized by dyspnea, cyanosis, and polycythemia. In view of the complete lack of definition it would seem desirable to avoid the use of this term or to limit it to the clinical syndrome.

RESULTS OF ALTERED PRESSURE; MECHANICAL DISTORTION

Atelectasis

The term atelectasis (imperfect expansion) refers both to the imperfect expansion of pulmonary parenchyma at birth ("congenital" or "primary atelectasis") and to the collapse of all or any portion of the previously aerated lungs at any later period of life.

Atelectasis Neonatorum.—The failure of the lungs to expand completely after respiration is established is often due to insufficient vigor of respiratory movements in a weak, premature infant. Another common cause is obstruction of bronchioles by mucus, desquamated epithelium, and vernix caseosa, aspirated with the amniotic fluid by intrauterine respiratory movements or during the first inspiratory efforts after birth. Some degree of atelectasis may be found in the lungs of any infant dying during the first few weeks of life and is not considered to be pathologic unless it affects major portions of the lungs.

The unexpanded portions are located dorsally and the lower lobes are involved to a greater degree than are the upper lobes. On the pleural surface the atelectatic lobules are darker and depressed below the level of the aerated portions. On section they are purplish red, sharply delimited, and fleshy but not firm. The microscopic appearance is that of fetal lung, lacking

clearly defined alveolar structure in those areas which have not been expanded. The parenchyma appears as a maze of tortuous capillaries interspersed with numerous rounded or polyhedral septal cells. If partial expansion has occurred, the lumina of alveolar ducts and alveoli may contain coagulated protein, desquamated squamous epithelium, and, occasionally, hyaline membranes, formed by flattening of lipid substance (*vernix caseosa*) against the walls of respiratory bronchioles and alveolar ducts (Fig. 522). The columnar epithelium of the bronchioles is infolded and the lumen is H-shaped.

Secondary Atelectasis.—The commonest mechanism which operates to produce collapse of small masses of parenchyma is that of absorption of air in a lobule or group of lobules after the bronchioles which supply them have been obstructed. Plugs of thick mucus and swollen mucosa in infectious bronchitis of childhood most frequently are responsible for the obstruction. The other principal mechanism is that of compression of the lung from the outside by fluid, air, or solid masses such as tumors. The accumulation of large quantities of fluid in the thoracic cavity, due to circulatory disturbances or inflammation, and the introduction of air in the therapy of tuberculosis are among the commoner causes. Various degrees of compression atelectasis are encountered in routine post-mortem examinations in the presence of obesity or abdominal distention from any cause where the arch of the diaphragm is displaced upward to such a degree that the base of the lung is compressed. Neoplasms of the lung or mediastinum may bring about atelectasis by compression, by obstruction of bronchi, or by both mechanisms.

Atelectatic tissue does not crepitate when squeezed, the areas are dull red to purple-red (or blue when viewed through the pleura) and depressed below the level of surrounding aerated tissue both on the pleural surface and on surfaces made by section. The tissue is compressible, in contrast to masses of exudative consolidation, and comparatively dry, yielding only a little bloody fluid on sectional surfaces. When due to bronchial obstruction, the masses are roughly pyramidal in shape, with base on the pleura and apex formed by the obstructed bronchus or bronchiole. In microscopic sections, the walls of alveoli, alveolar ducts, and respiratory bronchioles are closely apposed and the spaces slitlike, paralleling each other (Fig. 521). Bronchioles within the area are infolded and their lumina more or less completely obliterated unless filled with mucus or exudate. The alveolar capillaries appear to be dilated, but it has been shown by controlled experiments that less blood flows through an atelectatic lung than through a normally expanded one. In the presence of inflammation, organization takes place in collapsed pulmonary tissue, permanently obliterating the air spaces, but in the absence of infection, re-expansion is possible even after years of collapse. The change which most often prevents re-expansion of the lung after prolonged therapeutic pneumothorax is thickening and rigidity of the pleura rather than fibrosis of the parenchyma.



Fig. 520.—Bilateral massive collapse of lungs in 18-month-old infant, following aspiration of mucus and clotted blood during surgical operation. Only the ventral margins of the lungs are aerated.

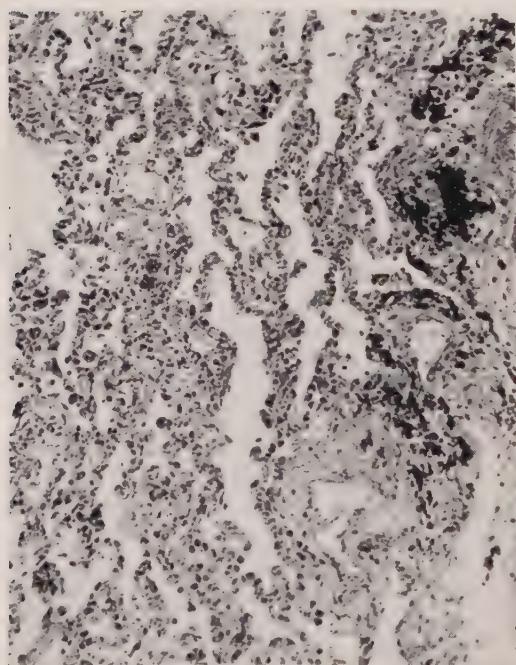


Fig. 521.

Fig. 521.—Atelectasis in adult lung from compression by intrapleural fluid.

Fig. 522.—Fetal atelectasis. The unexpanded alveoli contain squamous epithelial cells, aspirated with amniotic fluid.

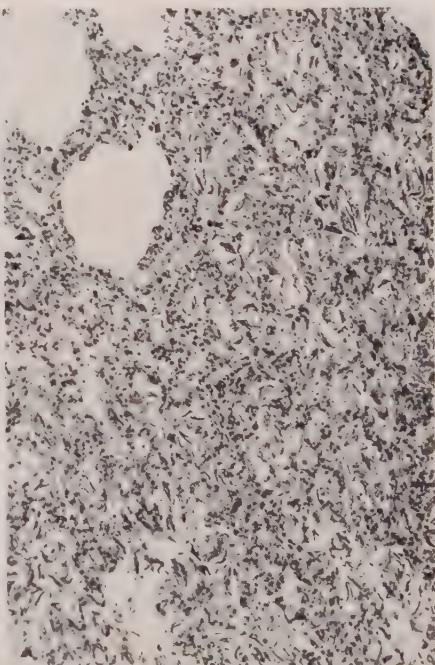


Fig. 522.

Acute Massive Collapse.—Acute massive collapse of the lung is a form of atelectasis involving a lobe or an entire lung (Fig. 520). It is the result of abrupt complete obstruction of a large bronchus or of rapidly developing pneumothorax. The accident is usually observed as a complication of surgical operations on the abdomen, a plug of mucus obstructing the bronchial lumen. The plugging of a bronchus by an aspirated foreign body may have the same result. Since the volume of the lung is reduced, the mediastinum is displaced toward the affected side. If the obstruction is relieved by coughing or by surgical removal of mucus or a foreign body, the collapsed lung or lobe re-expands rapidly, with prompt relief of respiratory difficulty.

Emphysema

This term is derived from a Greek word meaning inflation. As applied to the lungs it means either overinflation of the

adequately described the condition as a clinical and pathologic entity, is very common, being observed in 2 to 5 per cent of cases coming to autopsy. In tropical countries, it appears to be much more common than indicated by these figures, but the reason for this distribution is unknown. It is more common in men than in women, due in all probability to the much higher incidence of bronchial infections in men.

MORBID ANATOMY.—The lungs in chronic emphysema are diffusely involved but the degree of distention is not always uniform. The lungs are pale, voluminous, and like a soft feather pillow in consistency. Instead of collapsing when the pleural space is opened at necropsy, they remain dis-



Fig. 523.—Interstitial emphysema in lungs of newborn infant. Mouth-to-mouth insufflation was done in an attempt to revive the infant.

air chambers ("vesicular") or the escape of air into the loose connective tissue of lungs and pleura ("interstitial"). A moderate degree of acute hyperinflation of alveoli is compatible with complete restoration of size of the chambers and of normal function when the cause of the distention is removed, but prolonged distention is associated with loss of elasticity and permanent deformity of the parenchyma.

Diffuse Vesicular Emphysema.—Diffuse vesicular emphysema or "true emphysema" in the sense of Laennec, who in 1819 first

tended, not only filling the cavity but often protruding from it, their margins meeting in the midline in front of the heart. All portions may be affected, but the deformity is exaggerated in the apices and sharp margins, especially of the upper lobes. In these margins many air sacs are disproportionately distended with the formation of bubblelike bullae, varying from a few millimeters to several centimeters in diameter. When compressed, there is no elastic rebound; the depression produced by the examining finger remains on the surface. Instead of the fine crepitus

experienced in examining the normal lung, there is a sensation of rupturing many delicate cysts.

Microscopic examination of tissue from uncomplicated emphysema shows greatly enlarged and deformed air spaces of unequal size, with relatively few open capillaries in the alveolar walls. Respiratory bronchioles, alveolar ducts, and their related alveoli are ballooned out to a degree

interalveolar pores. Actual rupture of alveolar walls also takes place as proved by the presence of blebs beneath the pleura. Blebs are pockets of air between the pleura and parenchyma, formed by the rupture of air sacs, allowing air to escape into the subpleural space.

Dilatation of the bronchioles extends centrally to tubes of about 2 mm. in diameter. In obstructive emphysema, bron-



Fig. 524.—Bullous emphysema of adult lung. Anthracotic pigmentation of pleura.

which destroys their identity as separate structures and makes each functional unit appear as one large, slightly irregular cyst with blunt spurs (suggesting ruptured alveolar walls) projecting into the common lumen (Fig. 525). There is no actual loss of elastic tissue in simple emphysema, but, due to the stretching of the tissue, the fibers as well as the septal capillaries are more widely spaced. Examination of thick sections shows greatly enlarged

bronchioles which would normally vary between 3 and 8 mm. in diameter, often show muscular hypertrophy, a thickened mucosa, and a narrow lumen.¹¹ This is constantly found in the emphysema of chronic bronchial asthma. Many variations occur, however. The reasons for the variety of picture will be clear from a consideration of the pathogenesis of emphysema.

PATHOGENESIS.—When the lumina of lobular bronchioles are completely obstructed, the air

within the related air spaces is soon absorbed and the affected lobules become atelectatic. If the obstruction is not quite complete, allowing some air to pass the obstruction during deep, vigorous inspiration, emphysema of the related lobules is the result. The mechanics of obstructive emphysema are not entirely clear, but, in the case of obstructing mucus and mucoid exudates, a reasonable explanation can be offered. During inspiration, small bronchi and bronchioles are both dilated and elongated as the elastic force of the lung is overcome. Inspissated exudate in the lumen adheres to the walls, and the force of inspiration draws some air past the partly relieved obstruction into the air spaces. Expiration in normal quiet breathing is largely passive, depending upon the elastic recoil of the lungs and the relaxation of the diaphragm. The bronchi again become shortened and narrowed, their contained exudate again filling the lumen so that the air in the alveoli and respiratory bronchioles becomes entrapped. Since the air cannot be absorbed by the blood as rapidly as it is replenished by inspiration, the sacs are constantly distended so long as the partial obstruction persists. If the bronchioles are diffusely involved, the subject suffers from air hunger and the degree of hyperdistention is aggravated by forceful inspiration.

Another mechanism commonly operates to produce emphysema of limited extent, in the absence of partial obstruction of bronchiolar lumina in the affected areas. This consists of a diminution of volume of a part of the parenchyma. The loss of volume resulting from the collapse of numerous small masses of tissue can be compensated by the moderate expansion of the rest of the lung, but if the mass involved is extensive, as in the obstruction of a main bronchus of a lobe or in the obstruction of numerous small bronchi, the remaining lung with open tubes will be expanded to perhaps twice its normal volume or more. Examples of acute "compensatory" or "complementary" emphysema are seen, particularly in children, in many acute inflammatory diseases of the lungs where bronchial exudate produces obstruction and extensive focal atelectasis. In these cases, masses of atelectatic tissue alternate with masses of emphysematous parenchyma. The aspiration of foreign bodies, blood, or exudates may prevent air from entering many lobules and, aided by more or less violent inspiratory efforts, the adjoining nonobstructed lobules or the entire remaining open lung tissue becomes overdistended. If the obstruction affects bronchi of the second or third order, as in aspiration of foreign bodies, massive collapse affecting one or more entire lobes will be followed by acute emphysema not only of the unobstructed portions of the affected side but also of the opposite lung with displacement of the mediastinum to the side of the atelectatic lobes. Chronic emphysema may be produced by this same mechanism if the obstruction remains long unrelieved.

COMPLICATIONS.—The more serious complications of emphysema are associated with acute obstructive forms which develop in the course of postinfluenzal and other severe bronchopneumonias and occasionally with obstruction by aspirated foreign bodies. Blebs formed under the pleura

may rupture with the development of pneumothorax. The rupture of distended air sacs into the peribronchial connective tissue leads to interstitial emphysema of lung and mediastinum. Either of these accidents is serious and often fatal since the pulmonary circulation and the external respiration are further disturbed. Hemoptysis from simple rupture of alveolar walls is not common in emphysema.

The complications of chronic obstructive emphysema are dependent upon the increased arterial pressure, cardiac hypertrophy and failure which develop in the more extreme cases.

Senile, Postural, or Small Lung Emphysema.—This is a type commonly found in routine autopsies in the aged and less frequently in younger people. It is often associated with deformities of the thorax. The thorax may be increased in its anteroposterior diameter as in obstructive emphysema, or one side of the thorax may be enlarged at the expense of the other with compression of one lung and overinflation of the other. Kountz and Alexander¹² found, in the cases which they studied, stiffness and a more vertical position of the thoracic spine with a tendency to elevation of the ribs ("barrel chest" deformity). The diaphragm is not pushed downward as in obstructive emphysema, there is no great enlargement of the lungs, and impairment of respiratory function is usually slight or absent.

Pulmonary Interstitial Emphysema.—When alveoli and respiratory bronchioles are abruptly overdistended, air may escape into the delicate loose connective tissue which surrounds the pulmonary blood vessels and into the interlobular septa and pleura. Macklin¹³ has shown experimentally that the air which breaks through into the perivascular sheaths, travels along these sheaths into the hilum of the lung and thence into the mediastinum. When the flow of air is abundant, considerable pressure may be exerted on the vessels, restricting the flow of blood. This form of emphysema used to be seen more commonly than now in newborn infants upon whom mouth-to-mouth insufflation had been tried in order to induce them to breathe (Fig. 523). Similar changes often follow the use of pulmators in asphyxiated persons. The aspiration of foreign bodies is another important but less common event which leads to the development of interstitial emphysema. These may be designated as traumatic forms of the disease. Most cases develop in children as complications of acute focal emphysema in the course of acute or subacute bronchitis and bronchopneumonia.

Bronchial Asthma.—

ETIOLOGY AND PATHOGENESIS.—Bronchial asthma has no one specific cause, but the symptom complex and pathologic alterations of the tissue are common to all cases of true asthma. It is based upon tissue hypersensitivity to a wide variety of foreign substances, either bacterial or nonbacterial, which can act as antigens. The tendency to develop hypersensitivity in pathologic degrees is inheritable. It is assumed that all cases of true bronchial asthma are based upon specific hypersensitivity to one or more antigens although it is not possible in every case to

identify the specific substance. All age groups are affected. The manifestations when occurring in young children are often temporary, attacks becoming less frequent and disappearing entirely as the affected individual matures. In adults, the hypersensitive state usually remains for life with remissions and exacerbations, relief being obtainable by removing the patient from all contact with the antigen to which he has become hypersensitive. When the offending substance is a pollen, the attacks are seasonal as in hay fever. Foods such as milk, eggs, and cereals are regarded by some as important causes, especially in childhood. Proteins of bacteria harbored in the patient's own respiratory tract are thought to be contributory in many of the adult cases.

(barrel-shaped chest). Death rarely occurs from uncomplicated asthma. Terminal bronchopneumonia is frequent, as it is in many chronic debilitating diseases. Increased resistance in the pulmonary circulation is an essential part of diffuse vesicular emphysema and is constantly associated with hypertrophy of the right ventricle of the heart in long-standing cases. Cardiac failure is sometimes one of the late results.

MORBID ANATOMY.—The lesions in the lungs of asthma victims dying during an acute attack consist mainly of vesicular emphysema, and of thickening of the walls of bronchi and bronchioles with obstruc-



Fig. 525.

Fig. 525.—Vesicular emphysema. Microscopic picture in a long-standing case of bronchial asthma.

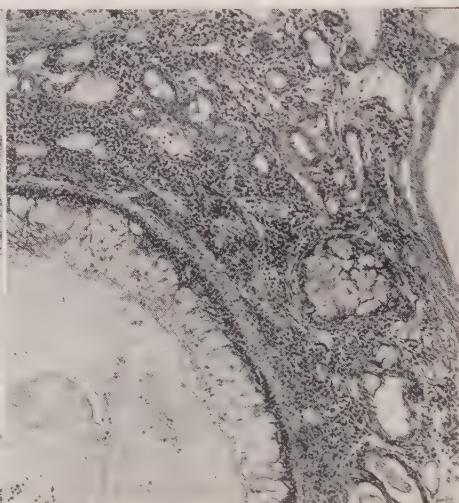


Fig. 526.

Fig. 526.—Bronchial asthma. The bronchiolar wall is densely infiltrated with lymphocytes and eosinophiles. The goblet cells are distended and the lumen is filled with mucus.

Until the disease is far advanced, asthmatic individuals are entirely well between attacks and, if permanently removed from contact with the substance to which they react abnormally, show no evidence of disease. The principal symptom is usually abrupt in onset and consists of severe dyspnea, characterized by difficult prolonged expiration. This is attributable to partial obstruction of the lumina of small bronchi and bronchioles. One of the factors of obstruction is probably a spasmotic contraction of the smooth muscle of the bronchioles. The evidence obtained from postmortem examination of the lungs of those dying during an acute attack supports the view that inflammatory thickening of the mucosa and obstruction of the lumina by thick tenacious mucus are of more importance in fatal cases than is bronchiolar spasm. This gradually leads to permanent over-distension of the lungs with loss of elasticity (emphysema) and tendency to fixation of the chest wall in the position of deep inspiration

tion of their lumina by inspissated mucus. The trachea and large bronchi are little affected and, at most, show diffuse reddening of their lining. Thickening of the bronchi is due to edema, cellular infiltration, and fibrosis, which affect all layers. The muscle is usually found in a state of contraction, but whether it commonly shows true hypertrophy is a matter of dispute. The epithelium shows increased height and pseudostratification. Desquamation is ordinarily moderate and ulceration absent in the cases uncomplicated by secondary infection. The basement membranes of medium-sized bronchi are thickened and hyalinized. The glands are large and show evidence of increased rate of

production of mucinous secretion. The connective tissue of the mucosa and submucosa shows moderate edema and is infiltrated by lymphocytes, monocytes, and eosinophiles. Eosinophilic leukocytes are extremely numerous in some cases, but few or absent in others. Their significance is unknown.

The mucus which fills the lumina of many of the tubes contains desquamated epithelial cells, monocytes, and eosinophilic leukocytes in variable numbers (Fig. 526). Toward the end of an attack, these masses are coughed up and expectorated. The content of the sputum varies but practically always shows plugs of inspissated mucus, monocytes and macrophages, degenerated epithelial cells, and some leukocytes. The more pathognomonic elements are eosinophiles, Curschmann's spirals, which are the twisted spirals of mucus from the bronchioles, and Charcot-Leyden crystals. The crystals are of protein constitution and the best evidence to date points to their origin from the nuclei of eosinophiles with which they are invariably associated.¹⁴ In the parenchyma of the lungs there is much hyperdistention, with rupture of alveolar walls in many places. The enlargement of air sacs is unaccompanied by any thickening or fibrosis of septa unless the lung has also been the site of an inflammatory process. Sometimes the emphysematous tissue is interspersed with small patches of atelectasis resulting from long-standing complete obstruction of small bronchioles.

Bronchiectasis

ETIOLOGY AND PATHOGENESIS.—The permanent dilatation of a bronchus or group of bronchi tends to occur in the smaller tubes, distal to a site of obstruction of the lumen. Eighty per cent of cases have their beginning in childhood.¹⁵ The disease is invariably associated with destructive inflammatory processes by which bronchial musculature and elastic fibers are weakened or completely destroyed and epithelium is damaged to an extent which impairs evacuation of secretion and exudate by ciliary action. Accumulation of decomposing exudate prolongs irritation and promotes infection in the over-distended tubes. These two factors, infec-

tion and hyperdistention, are thought to be most essential in the pathogenesis of the disease.

A distinction is drawn between the congenital cystlike deformity of the bronchi known as congenital lung cyst and postnatal dilatation of bronchi or true bronchiectasis, although it is difficult to disprove the hypothesis that congenital weakness of the bronchial musculature and elastic tissue may predispose to dilatation later in life under the stress of mechanical forces and the weakening influence of infection. The nature of the obstruction in a small number of cases is impacted foreign body, adenoma within a bronchus, or compression of a bronchial wall by an enlarged caseous lymph node. More frequently the local destruction of bronchial mucosa by malignant neoplasms leads to the accumulation of mucus and cellular debris in the dependent portions of the bronchial tree distal to the partial obstruction, and to unilateral bronchiectasis, accompanied by cough and copious expectoration. In the great majority of cases, the less spectacular obstruction by inspissated mucus and exudates incident to the bronchial infections of childhood is responsible. Gladys Boyd¹⁶ found bronchopneumonia to be the commonest form of disease which provided the conditions for bronchial dilatation in childhood. A physiologic block may result from damage to ciliated epithelium or from squamous metaplasia of epithelium, especially in the dependent portions of the lungs where the effects of gravity tend to prevent evacuation of the lumina.

There are some cases, however, in which evidence of obstruction is lacking. In an attempt to explain these, some writers (Andrus,¹⁷ Ogilvie¹⁵) favor the idea that a most important mechanical factor is the excessive pull of the elastic parenchyma upon the walls of bronchi when the surrounding tissue is atelectatic. Tannenberg and Pinner¹⁸ found that, under experimental conditions, externally applied stresses have no appreciable effect upon the dilatation of the bronchi. Dilatation occurred as well when the elastic pull was nullified by artificial pneumothorax as in the absence of pneumothorax. In human cases, it is true that atelectasis is often present in the affected lung. Infection provides the stimulus for hypersecretion of mucus and for exudative inflammation. Inspissation of mucus and exudate leads to bronchiolar and bronchial obstruction, and this is followed by collapse of related parenchyma and bronchioles. If to the obstruction is added destructive inflammatory disease, the cleansing action of the cilia is abolished, exudate accumulates in the lumen, and the tubes thus affected become distended. Tannenberg and Pinner observed that complete atelectasis occurred within two to four hours after bronchial obstruction was effected. Complete atelectasis could exist in the experimental animal up to several months without the occurrence of complicating processes, but when infection was added, bronchiectasis was the common result.

The bacteria most commonly isolated from the exudates of bronchiectasis are those which

are responsible for the acute infectious process of which bronchiectasis is a sequel, and often these are mixed with some of the common flora of the upper respiratory tract. Those most often reported are streptococci,¹⁹ Pfeiffer's bacilli,²⁰ and fusospirochetal organisms.²¹ Most authors find no specific bacteria in constant relationship to bronchiectasis.^{22, 23}

Most examples of advanced bronchiectasis are found in the lower lobes and especially in the vertically aligned bronchi of the dorsomedial portion of the base. When the upper portions of the apical lobes are affected, the associated disease is usually tuberculosis. While bronchial obstruction undoubtedly plays some part in these, the small saccular and club-shaped cavities are probably formed by necrosis and excavation of the parenchyma rather than by simple dilatation of bronchioles.

and stiff, the mucosa thick, hyperemic, soft, and sometimes rugose, but not conspicuously ulcerated in the majority of cases. The lumina are usually filled with mucopurulent exudate. Erb²³ observed destruction with ulceration during the early stage, followed by a stage of repair which was not much in evidence until six weeks had elapsed. The parenchyma immediately surrounding the dilated bronchi is partly or completely atelectatic and fibrosis is usually present as a result of organization of exudate.

The histologic findings vary with the cause and chronicity of the process. The

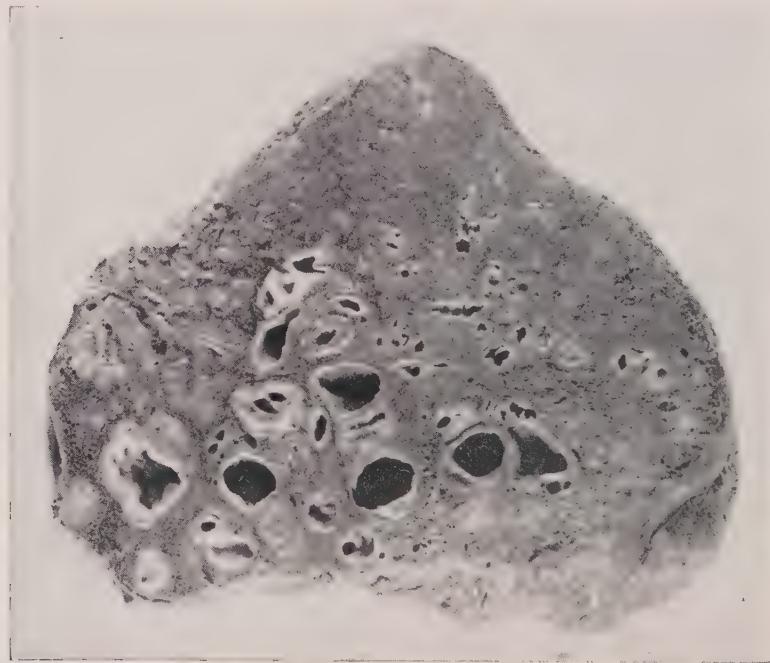


Fig. 527.—Bronchiectasis. Lower lobe of child's lung removed surgically. Bronchiectatic abscesses, lower left of figure.

MORBID ANATOMY.—Minor degrees of bronchiectasis are not easily recognized in the collapsed lung at the autopsy table and are best demonstrated by sectioning with a sharp knife after hardening by insufflation of the bronchi with fixing fluid. Thin-walled bronchioles may show a diameter of several millimeters as they are followed out to within a few millimeters of the pleura. The common form is tubular or club-shaped, but saccular and fusiform enlargements are recognized. In the typical cases the tubes are much thickened

mucous lining often consists of thickened columnar epithelium showing pseudostratification and sometimes squamous metaplasia. The fibrous wall usually is poor in elastic fibers and muscle. Often, the muscular wall is entirely replaced by connective tissue, infiltrated with the cells of chronic inflammation. No sharp distinction can be made between the end result of simple dilatation of chronically inflamed bronchi and those cavities which have been produced by destruction of bronchial walls and surrounding parenchyma

and which have acquired an epithelial lining during the stage of repair. A fibrous wall of uneven thickness, devoid of muscle and glands and infiltrated with lymphocytes, monocytes, and plasma cells, is the end result in either case.

Air-Blast and Water-Blast Injuries of the Lung

When persons are exposed to the effects of near-by explosions of bombs or aerial torpedoes, death may occur in the absence of any marks of violence on the outside of the body. Hemorrhage of the lungs is usually found, varying from a few punctate or macular hemorrhages on the surface of the pleura to extensive extravasations into the parenchyma. In most cases the injury to the lungs is insufficient to account for death. The distribution of the hemorrhages is irregular, but often they appear in the costomediastinal and costophrenic angles and sometimes the pleural hemorrhages follow the lines of the ribs. Histologically, rupture of alveolar walls and more or less extensive intra-alveolar and interstitial hemorrhages constitute the principal lesions.

The effects of water blast, suffered by persons immersed in the sea during the explosion under water of bombs or torpedoes in the immediate vicinity, differ from those of air blast in that they do not ordinarily affect solid organs and tissues except those which contain gas. Tissues of the lungs and intestines are torn and hemorrhagic. (See also discussion on page 133.)

EXUDATION AND FIBROSIS DUE TO PHYSICAL AND CHEMICAL AGENTS

Chemicals; Heat.—Injuries of the laryngeal and tracheobronchial mucosa of sufficient severity to assume clinical importance are most frequently produced by infectious agents, but nonbacterial irritants, particularly gases and soluble dusts, are far from a position of minor importance in certain industries and in war. In civilian life, the injuries produced by chemically active gases differ more in degree than in specific nature and vary from mild transient laryngitis and tracheobronchitis to deep necrosis with ulceration of the mucosa and extensive exudative pneumonia. When injuries follow the inhalation of mixtures of gases from explosions and conflagrations, it is difficult or impossible to determine the nature of the injurious agents. It has been thought that heat alone may be responsible for severe injury to the respiratory tract and to the parenchyma, but experimental evidence is against this view.²⁴

Radiation Pneumonitis.—The application of x-ray irradiation to the therapy of deep-seated lesions of the lungs and mediastinum has given rise to lesions of pulmonary structures, the chief of which is fibrosis of the pulmonary parenchyma (see page 179).

Lipid Pneumonia.—The importance of aspirated oils in the production of human disease was called to the attention of physicians in

1925 by Laughlin.²⁵ The subject was investigated intensively by animal experiment and chemical studies two years later by Pinkerton.²⁶ Many cases of lipid pneumonia in infants, older children, and adults have been described in the literature since that time, and additional experimental studies have been made. The reaction of the tissues to the presence of irritating oily substances is characteristically macrophagic and proliferative. The extent of the lesions and degree of fibrosis are determined by the quantity and chemical constitution of the oil which is introduced into the parenchyma and the time over which it acts. The oils which have been implicated in the greatest number of cases are cod-liver oil in infants and mineral oil in adults. In general, the simple neutral vegetable oils such as Lipiodol (iodized poppy-seed oil), sesame oil, and olive oil excite very little reaction in the tissues and are slowly absorbed with little residual fibrosis. Some of the animal oils cause marked fibrosis and giant cell formation within a matter of days.

Liquid petrolatum becomes emulsified and the fine droplets are phagocytized by macrophages which accumulate in large numbers at the site, filling the air spaces. A reticulum of collagenous fibers is laid down between the foamy macrophages, and the phagocytized oil becomes fixed by the immobilized phagocytes and the fibrous tissue which forms. The oil can be differentiated from others by its failure to react with osmic acid while staining with scarlet red and, faintly, with nile blue sulfate. Such a lesion is practically permanent, constituting a tumorlike mass of granulomatous tissue into which little or no air can enter and called by some writers "paraffinoma."²⁷ The greatest number of these formations are found in adults, particularly in the aged who use medicated mineral oil as nose drops or sprays, usually self-administered. The gross form of the lipid areas may be anything from small, poorly defined granulomatous nodules in the dorsal parts of the lungs, to complete homogeneous consolidation of an entire lobe. The lesions are frequently bilateral but tend to affect the right lung more extensively than the left and the lower lobes more than the upper. A patient lying flat on his back during the administration of an oily substance will show areas of consolidation in dorsolateral portions of the upper lobes in the areas of distribution of the dorsal rami of the upper lobe bronchi. Bland oils do not excite the cough reflex and flow readily from the pharynx into the larynx and thence to the dependent portions of the lungs. Although the quantity reaching the parenchyma at any one time is relatively small, daily administration over a period of years permits accumulations which have been estimated as high as 100 c.c. and more.

Cod-liver oil, halibut-liver oil, cream, and other of the more or less irritating oils of animal origin are found in the lungs of infants more often than in older children or adults. Normal infants are occasionally affected when oil, most commonly cod-liver oil, is administered against resistance, as by holding the nose in order to force the child to swallow. The commoner circumstances are in small weak infants

whose swallowing act is in some way defective, those in which regurgitation or repeated vomiting occurs, and in the presence of cleft palate, pharyngeal paralysis, idiocy, or comatose state. Since such infants are usually fed in the upright or semireclining position, most of the aspirated substance will flow into the lower lobes.

The disease is practically symptomless until secondary bacterial infection of the lungs is superimposed, and then the clinical and x-ray findings are those of a low-grade bronchopneumonia which does not resolve or resolves very slowly over a period of months. When death occurs, it is usually the result of superimposed bacterial bronchopneumonia. The diagnosis is rarely made before death but should be suggested by a history of often repeated administration of oils with opportunity for aspiration of them and by the finding of x-ray evidence of pulmonary consolidation which fails to resolve. The sputum sometimes contains droplets of oil and lipid-filled macrophages but rarely is of much assistance in establishing the diagnosis.

ing fibrin.²⁸ This substance is relatively insoluble in the ordinary staining reagents, is acidophilic and acid-fast, and acts as a foreign body in the tissue. Particles of it are found within the macrophages at a later stage. The reaction to the oil which follows the acute exudative phase is monocytic and macrophagic. Fibrosis is not so conspicuous as in the case of mineral oil. Multinuclear giant cells are more numerous. In the absence of bacterial infection, resolution with slow absorption of the oil takes place, but probably not without some residual thickening of alveolar walls and fibrosis. Cod-liver oil stains well with scarlet red, nile blue sulfate, and reacts with osmic acid to produce a black insoluble precipitate.

Pneumoconiosis

Mineral dusts, vegetable fibers, and even finely divided particles of animal origin are taken into the lung with the inspired air, but only the finest reach the respiratory bronchioles and air sacs, the

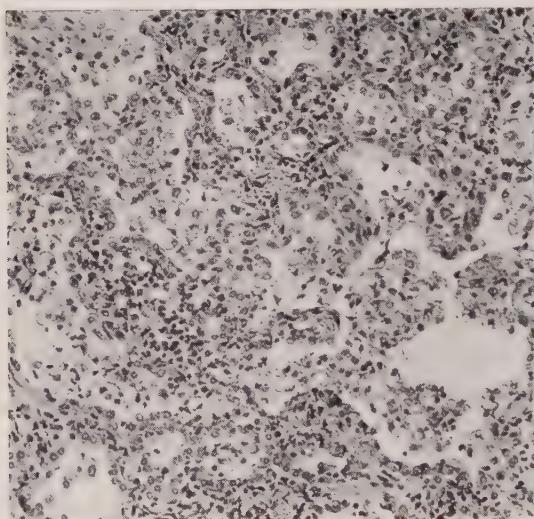


Fig. 528.

Fig. 528.—Lipid pneumonia in infant. Low-power photomicrograph.

Fig. 529.—Lipid pneumonia. Foam cells in alveolus and thickening of alveolar wall.

Fig. 529.

The yellowish appearance of the lung, together with its solidity and absence of pleural exudate or adhesions should suggest the diagnosis at postmortem examination. In the long-standing case with much fibrosis or in the case complicated by extensive terminal bronchopneumonia, the pathologic diagnosis cannot be made with certainty until suitable microscopic sections are studied.

The tissue reaction to cod-liver oil is characteristic and differs from that of mineral oil in several respects. Around the oil in the alveoli a hyaline membrane forms within a few hours, apparently from an interfacial reaction between the unsaturated oil and mixed proteins, includ-

rest being expelled with the mucus in which most particulate matter becomes entangled. The dust which reaches the parenchyma is phagocytized by alveolar macrophages, disposed of by intracellular digestion when this is possible or, if insoluble, becomes aggregated within the parenchyma or in the interstitial tissue, especially of the lymphoid nodules. If completely insoluble in the tissues, as is carbon, very large accumulations may be fixed in the lung without appreciable im-

Continued on page 672

pairment of function. Of the irritating dusts, silica has the greatest importance and is found in various concentrations in most of the dusts which are active in producing fibrosis of the lung.

Silicosis.—The fibrosis of the lung which results from the presence of finely divided silica (SiO_2) is both diffuse and nodular. The miliary nodulation seen early in the disease and the coarse, coalescent nodules of the advanced stages serve to distinguish silicosis from all other dust diseases. The tendency to form discrete nodules is greatly enhanced by coexistent tuberculous infection. The rapidity of development of the disease depends upon the amount of dust in the inhaled air, the amount of silica in the dust, and the duration of exposure. The fineness of the dust is an important factor since its solubility is proportional to the surface area exposed to the tissue fluid. The finer the particles, the greater the damage.

The disease, in pure or modified form, occurs most commonly in workers in the mining industries, gold, iron and coal mines, in stone workers, in metal grinders and polishers, in sand blasters, and, in short, in any occupation which subjects the worker to breathing an atmosphere heavily loaded with silica-bearing dusts. Clinically the disease is divided arbitrarily into stages, based upon severity of symptoms and extent of fibrosis of the lungs as visualized by x-ray examination. The earliest symptoms of shortness of breath and dry cough commonly appear only after ten to fifteen years of exposure and are determined by deficient aeration of the blood and irritation of tracheobronchial mucosa.

In exceptional circumstances, symptoms may appear within two or three years of the beginning of very heavy exposure.²⁹ These are classified as acute silicosis. Pathologically they differ from the chronic form in that the lesions are very fine and the fibrosis much more diffuse than is the common type. The earliest visible nodules appear at the periphery of the lung just beneath the pleura and around the smaller bronchi and blood vessels. By the time fibrosis is sufficiently extensive as to be visible in x-ray films, the distribution is extensive throughout the substance of both lungs and is fairly

symmetrical, appearing as fine irregular mottling in both lung fields (Fig. 530). Later the fibrotic areas produce a generalized coarse mottling, which is usually denser in the middle one-third of the lung fields. By the time this intermediate stage is reached, the symptoms usually indicate serious disease. A dry cough, shortness of breath on slight exertion, chest pain, night sweats, and hemoptysis are the most characteristic. In the advanced stages the lung markings in x-ray films are largely obliterated by extensive coalescent areas of great density.

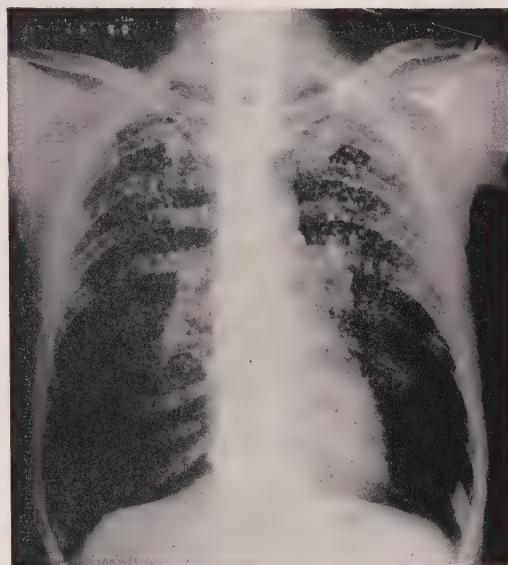


Fig. 530.—Silicosis. Roentgenogram of lungs showing distribution and relative density of lesions.

At necropsy the almost solid lungs are removed from the chest with great difficulty on account of fibrous adhesions which cover it on all surfaces. The pulmonary substance is so dense that it offers resistance to cutting comparable to that of tire tread rubber. Sectional surfaces show gray airless masses of various shapes and sizes, most of the discrete nodules having been obscured by coalescence of fibrotic areas. Between the completely solid airless tissue there are masses of emphysematous tissue (Fig. 531). In such extreme cases, the tracheobronchial lymph nodes are enlarged and solidly fibrous, closely resembling in color and consistency the solid portions of the

parenchymal lesions. In less advanced cases, discrete nodules resembling the fibrous tubercles of healed tuberculosis are found in them. Uncomplicated silicosis occasionally shows areas of necrosis and cavitation, but the lesions of silicosis so closely resemble those of tuberculosis and the two diseases so often coexist in the same lungs, that it is more conservative to consider an excavating lesion as tuberculous (silicotuberculosis) until

liberated particles. Epithelioid cells are formed by transformation of the smaller mononuclear cells into large pale cells with eccentric nuclei. Multinuclear giant cells, indistinguishable from those of tuberculosis, soon form in the cellular agglomerations within alveoli and in peritrunical lymphoid nodules. Smaller quantities of silica stimulate a purely proliferative reaction. Larger concentrations lead to inflammatory responses and necrosis. Polymorphonuclear leukocytes are found in important numbers only in the presence of necrotic lesions or of secondary infection. The specific nodules are formed wherever there is sufficient concentration of silica



Fig. 531.

Fig. 531.—Silicosis in lung of sand blaster. Lower lobe.

Fig. 532.—Anthracosilicosis. The concentration of pigment in the upper lobe was probably due to a once active tuberculosis. Apical scars are seen in the right upper lobe.
(Specimens in F. R. Zeit Museum, Northwestern University.)

proved otherwise by meticulous examination in appropriately stained sections of all of the lesions of both lungs.

Gardner³⁰ has demonstrated by animal experiment that silica can cause every type of cellular response which is found in tuberculosis. The first reaction to finely divided silica (particles of 1 to 3 microns in diameter produce the most typical reactions) is the invasion of the air spaces by mononuclear cells and phagocytosis of the inhaled particles. Both monocytes and alveolar macrophages appear to take an active part in ingesting and carrying the dust to distant foci. Some of the cells are killed by the effects of the silica. Other cells come in and pick up the cellular debris and

particles and an accumulation of phagocytes, by the local proliferation of fibroblasts, by the transformation of macrophages into fibroblasts or both. The ultimate result is the formation of laminated nodules, whorls, and irregular masses of coarse hyalinized collagenous fibers, encasing phagocytized or extracellular granules (Fig. 533). Pure silica is colorless and particles of 1 to 3 microns in diameter are not visible except under a polarizing microscope.

Modified Silicosis.—Mixtures of silica with many other substances in various proportions, when present in the lungs in sufficient quantities, can produce various degrees of diffuse or linear fibrosis, but the appearance of nodules is not conspicuous unless the concentration of silica is high. Mixtures of silica (SiO_2), silicates,

lime, carbon, and other constituents make up the dusts inhaled by workers in marble, granite, quartz, cement, coal, and talc, and by the users of numerous types of abrasives. Granite, for example, contains about 35 per cent of silica as quartz and over 60 per cent of silicates. The disease acquired from long exposure to granite dust (chalcosis) is characterized by the formation of linear lesions due to perilymphatic fibrosis.³¹

Siderosilicosis.—Iron dust can accumulate in large quantities in the lungs without producing any symptoms. Only when mixed with significant quantities of silica does serious disease result. Hematite miners' lung is very heavy and reddish brown in color if the pigment is predominantly hematite (ferric oxide mixed with low concentration of silica). Often the red color is masked by coal dust. Diffuse fibrosis is easily demonstrable but discrete nodules are uncommon.

Silicotuberculosis.—The observation that silicosis is an important accessory factor in clinical tuberculosis is supported by numerous animal experiments. In the presence of silica, tubercle bacilli reproduce much more rapidly in the tissues than in its absence,³² and strains of tubercle bacilli which ordinarily are avirulent lead to progressive disease and death of guinea pigs which have been made to inhale quartz dust.³⁰ Price³³ has shown that growth of tubercle bacilli is stimulated by the addition to artificial culture media of finely divided silica. The effect is apparently specific for silica and is not exhibited by dusts low in silica such as hematite and crude fluor spar or by nonsiliceous dusts such as marble, coal, and gypsum.³⁴

Since the cellular reactions and types of lesions produced in silicosis and tuberculosis are essentially the same (Gardner³¹), the modification of the infectious aspect of the disease con-



Fig. 533.

Fig. 533.—Silicotic nodules in lung. Low-power photomicrograph.

Fig. 534.—Diffuse fibrosis of the lung in asbestosis.

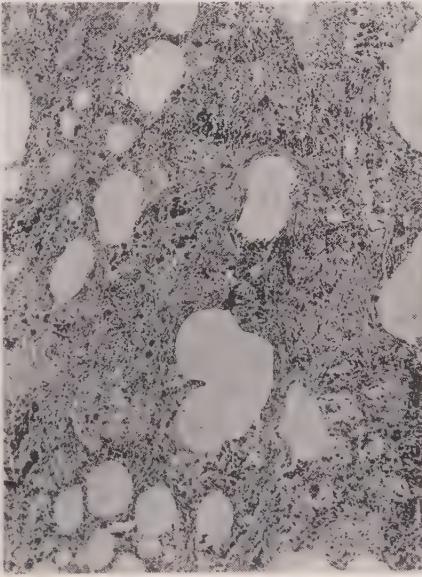


Fig. 534.

Anthracosilicosis.—Pure carbon is practically inert, and therefore the atmospheric soot of cities may be inhaled for a long lifetime without appreciable damage to the lung. Coal miners' lung is the result of inhalation over a long period of time of large quantities of coal dust mixed with various but usually small quantities of silica and other minerals. The fibrosis which often occurs is the result of irritation by silica and silicates and not by the carbon itself. The black pigment tends to be segregated at sites of chronic irritation and hence is found in greatest quantity in the dense scars produced by more irritating dusts or by infectious processes such as chronic tuberculosis (see Fig. 532).

sists merely in the enhancement of the progress of the disease. The presence of tuberculous infection in silicosis increases the tendency to formation of nodules. However, in the end stage, the forms of the nodular scars are so closely similar that the nature of the process can be determined only by the recognition of the compounds of silicon in the nodules with the aid of the polarizing microscope, by x-ray diffraction or by chemical analysis. Since the damage to tissue and the extent of lesions are dependent not upon the total quantity of silica but upon the rate of solution and therefore upon the size of the particles present in the tissue, the quantitative determination of SiO_2 in the tissue is not an accurate index of the pulmonary damage

sustained or of the relative importance of the dust as compared with that of coexistent tuberculosis.

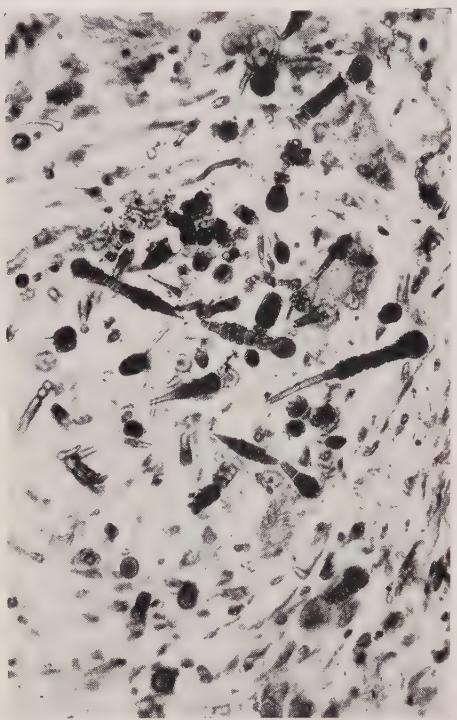


Fig. 535.—Asbestosis bodies. High-power photomicrograph from same lung as Fig. 534.

Bauxite Fumes.—In the manufacture of abrasives from calcined bauxite (alumina, clay, iron oxide, and titanium dioxide) the raw material is raised to high temperatures by electric current, releasing fumes which consist largely of ultra-microscopic particles of silica (29 to 44 per cent of fumes) and of alumina (41 to 62 per cent).³⁵ The inhalation of fumes by workers in the industry over periods of several years has been followed in a relatively small number of cases by diffuse fibrosis of the lungs. Most of the patients develop spontaneous pneumothorax and the mortality is high. The lesion differs from the usual picture of silicosis in that it is nonnodular, involves principally the central portion of the lungs, and shows pronounced peripheral emphysema with numerous bullae and pleural blebs.³⁶ Analysis of the lungs at autopsy has yielded concentrations of silica within the ranges usually found in silicosis.³⁵ In spite of the chemical evidence of significant concentrations of silica in the lungs and urinary excretion of silica as well as alumina, those engaged in the investigation of this industrial disease have avoided the conclusion that it is essentially an atypical form of silicosis because of the lack of nodularity of lesions. Experiments designed to elucidate further the possible influence of particle size (less than 1 micron in fumes), relative solubilities and the presence of alumina have been inconclusive.

The coating of quartz particles by aluminum hydroxide reduces their solubility and delays the fibrogenic effects³⁷ but does not prevent them.³⁸ While aluminum dust alone has not been proved by experimental means to possess fibrogenic properties, the prevalent opinion is that it plays some part in the genesis of bauxite fume disease. The aluminum dust disease which has been studied in Germany apparently presents a clinical and pathological picture similar to that resulting from exposures to bauxite fumes.³⁹

Asbestosis.—Disease due to the inhalation of the long fibers of asbestos is more often acquired by workers in the processing plants than in the asbestos mines where only the crude asbestos is handled. The fiber consists essentially of magnesium silicate and because of its relatively large size does not readily enter the alveolar sacs but ordinarily lodges in the respiratory bronchioles where the initial inflammatory reaction occurs. The fibrosis which results is diffuse (Fig. 534), rarely nodular, and involves the basal portions of the lungs rather than the middle portions as in the case of silica. The pleura is involved early, becomes greatly thickened and rigid, usually with obliteration of much of the pleural space by fibrous adhesions. Asbestosis bodies are pathognomonic of the disease and are thought to be formed by the deposition of proteins and the salts of iron on the surfaces of asbestos fibers. These are segmented, funguslike masses with bulbous ends and are yellow to orange-brown by transmitted light (Fig. 535). They are present in the air spaces, surrounded by macrophages and sometimes by multinuclear giant cells, or imbedded in the dense masses of fibrous tissue where all alveolar structure is obliterated. Occasionally the bodies can be found in the sputum, making possible a specific diagnosis. Lymph channels are not directly invaded in asbestosis since the particles are generally too large to be phagocytized and carried in the macrophages to lymph nodes. Therefore, the involvement of bronchopulmonary nodes is comparatively slight. Obliteration of lymph channels and blood vessels is brought about within involved masses of pulmonary parenchyma and pleura by the same mechanism which operates in any chronic inflammatory process, the swelling and proliferation of endothelium, followed by fibrosis. When the parenchymal involvement is extensive, reduction of the vascular bed with increased resistance to flow of blood through the lungs is followed by hypertrophy of the right ventricle of the heart ("cor pulmonale").

Berylliosis.—The most serious effects of beryllium in the human body are observed in the lungs and are the result of inhaling finely divided compounds of the metal by those engaged in the processing of beryllium ores and in the manufacture of fluorescent lamps. A few cases have been reported in nonindustrial contacts.⁴⁰ Beryllium metal, beryllium oxide, fluoride, sulfate, and hydroxide, and lamp phosphors ($ZnMnBeSiO_2$) have been implicated. Their concentration in the air and solubilities are important but not yet clearly defined. Acute diffuse pneumonitis of nonspecific character constitutes the early phase of the lesions and

does not differ from the acute inflammatory response to many other chemical agents except that it is nonnecrotizing. After a week or more the proliferative stage begins to replace the purely exudative. Large mononuclear cells predominate in the early stage; septal cells enlarge and exhibit various stages of desquamation; multinucleated giant cells appear and hyaline membranes are seen in some cases. The nodular or granulomatous stage arises by imperceptible gradation from the acute exudative stage. The nodules are formed by the fibroblastic organization of masses of exudate within the air spaces and alveolar septa. They may contain Langhans giant cells, basophilic (iron-containing) conchoidal bodies, similar to those of sarcoidosis, and rare asteroid inclusion bodies (Fig. 545). In the late fibrous stage the nodules tend to show a circumferential alignment of collagenous fibers but lack the whorls which are so often seen in silicosis (Fig. 536).

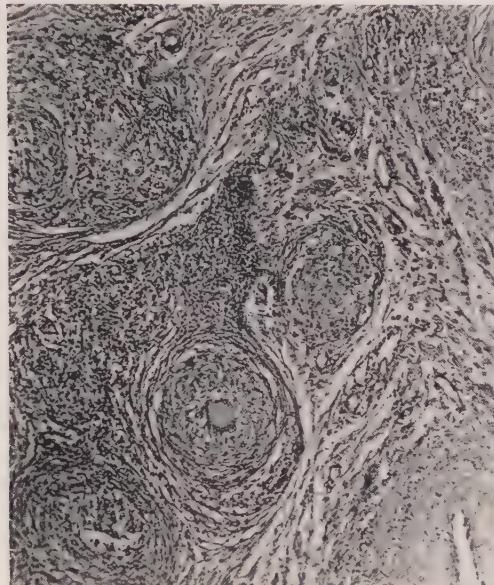


Fig. 536.

Fig. 536.—Nodular lesions of beryllium granuloma. Low magnification photomicrograph. Note lamination of collagenous fibers around central giant cell. (From lesion of subcutaneous tissue.)

Fig. 537.—Cadmium pneumonitis. The deformed alveoli are lined by hyperplastic septal cells and the air spaces largely occupied by masses of similar cells, including bizarre giant cells.

In advanced stages of the chronic disease, the lungs are voluminous and heavy. Invariably they are diffusely fibrotic but not uniformly so, areas of dense fibrosis alternating with honeycomb-like emphysema. Nodules ranging up to 2.0 mm. in diameter are usually scattered throughout the parenchyma and pleura. The lesions of lymph nodes are similar.⁴¹

The recognition of chronic berylliosis is by history of exposure, the finding of beryllium in the urine and by the histologic examination of involved lymph nodes. Similarly the granulomas which follow accidental introduction of

beryllium oxide or phosphors through the skin, as in cuts produced by broken fluorescent tubes, are easily identified by the characteristic granulomatous or fibrous nodules, the presence of granular necrosis but no true caseation, the absence or paucity of epithelioid cells, the presence of fluorescent granules,⁴¹ and the specifically stained granules of beryllium salts.⁴² Acute systemic effects from absorption of beryllium salts are chiefly in the liver which occasionally shows centrolobular necrosis.⁴³ (See also page 156.)

Cadmium Poisoning.—From the results of controlled experiments in laboratory animals and the chemical analysis of lung tissue from fatal cases in man, it has been estimated that the lethal dose of cadmium oxide inhaled as fumes is approximately 2,500 min. mg. per cubic meter. Appreciable quantities of cadmium are absorbed by organs and tissues other than the lungs and, since there is no

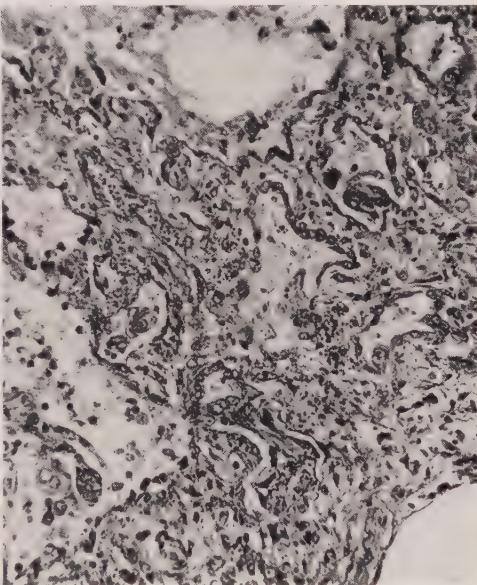


Fig. 537.

appreciable decrease in its content in pulmonary tissue for several weeks after exposure, it is probable that its presence in other tissues can be accounted for in large part by the ingestion of particles entrapped in the upper respiratory tract.⁴⁴ Experimentally the effects of the oxide and chloride are indistinguishable from each other and their demonstrable effects are found only in the lungs. A stage of acute congestion and edema, similar to that of acute phosgene poisoning, is followed by a stage of cellular proliferation in those animals which survive the effects of acute intoxication. The lesions of

two fatal human cases which have been reported by Bulmer, Rockwell, and Frankish⁴⁵ had reached the proliferative stage, the cases having survived for 5 and 8 days, respectively. By the eighth day the alveolar lining cells were swollen and hyperplastic, forming sheets of cells resembling epithelium (Fig. 537). These were continuous with similarly hyperplastic sheets of bronchiolar epithelium. Parenchymal edema persisted into the second stage but leukocytic exudate was scanty. The third stage, fibrosis, which has been observed only in laboratory animals, gradually replaces the actively proliferative stage. The residual fibrous tissue has been observed mainly to surround the larger bronchi and blood vessels, in contrast with the late effects of silicosis.^{45, 46}

VIRAL AND RICKETTSIAL INFECTIONS

Precise knowledge concerning the disease-producing effects of various filtrable agents is accumulating rapidly, but only a few distinct entities are clearly defined. Since in most cases these agents, acting alone, do not appear to have the power of causing fatal pulmonary disease in man, postmortem studies have yielded complex pathologic pictures varying with the nature of the secondary bacterial invaders. Experimental infections in susceptible animals furnish the only available material for studying the effects of pure viral infections. The lesions produced by various serologically distinct viruses have much in common. All predispose to secondary invasion by opportunist bacterial agents, many of which, unaided, lack the power to invade normal tissues. The ciliated columnar epithelium of the trachea and bronchi is damaged primarily, the first visible lesions sometimes beginning in the upper part of the respiratory tract and sometimes in the region of the bifurcation of the trachea, spreading upward toward the mouth and downward into the bronchioles as in influenza.

When the pulmonary parenchyma is invaded extensively, the exudate is characterized by much edema fluid, slight to moderate precipitation of fibrin, and a predominance of monocytes and lymphocytes instead of polymorphonuclear cells, in contrast with most bacterial infections. When the exudate contains a large quantity of blood, hemolytic streptococci are often found in it as in poststreptococcal and postinfluenza pneumonias. When fibrin is especially abundant and the pneumonic consolidation assumes a confluent lobular form, pneumococci are most frequently found to predominate in the lesions. Peribronchiolar abscesses usually indicate the presence of staphylococci, often of strains which have the property of hemolyzing blood.

The manner by which the viruses act to prepare the ground for bacterial invasion is still obscure, but there is no reason to doubt that there is such an effect or that it is of decisive importance. Many writers assume that the bacteria gain access to the lung through the walls of bronchi when the protective epithelium is lost. This easily accounts for the inflammatory reaction in the walls of bronchi-

and bronchioles but not for the mode of extension of the exudative process to the alveoli. Experimental evidence indicates a more direct route to the parenchyma through the lumen, by the mechanism of aspiration of liquid exudate and secretion from the lumina of the damaged bronchioles. Diseases caused by filtrable agents are discussed in a separate chapter (Rickettsial and Viral Diseases, page 299) and the emphasis in this section will be upon the results of mixed infections in the lungs, that is of bacterial diseases following viral damage, rather than upon the effects of viruses alone.

Coryza.—Of itself this usually mild disease does not constitute a serious danger to life and health. On the other hand, it appears to precede bacterial infections, particularly pneumococcal pneumonia, with a regularity which strongly suggests an important etiological role. Several possible mechanisms have been suggested. The most probable is that the abundant mucoseroous secretion from the inflamed mucosa increases the opportunity for pathogenic bacteria to be aspirated from mouth and nose into the air sacs beyond reach of the cilia.

Influenza.—The gross appearance of the tissues is not specific for influenza and may be simulated in other severe bronchopulmonary infections. The mucosa of the trachea is thick, soft, velvety, and deep red or purple. Thin gray pseudomembranes, consisting of necrotic epithelium and exudate, may remain on the surface. The lungs contain extensive, poorly defined areas of edema and hemorrhage, alternating with areas of emphysema. Pleural surfaces are mottled with purple areas, and are thinly coated over the involved areas with granular fibrin. Sectional surfaces show purple-red areas of hemorrhagic consolidation, sometimes with fine gray points at the sites of fibrin-filled, dilated alveolar ducts and alveoli.^{47, 48}

In the cases not complicated by severe bacterial infection, and not showing extensive exudative pneumonia, the involvement of the parenchyma is limited to narrow irregular zones of consolidation which appear to extend laterally from small bronchi and bronchioles along the septa of contiguous air spaces. This picture is common in viral diseases, pertussis, and other relatively mild bacterial infections of bronchioles and is frequently designated as "interstitial bronchopneumonia."*

The initial swelling and degeneration of mucosal cells is accompanied by excessive secretion of mucus and desquamation of epithelium, followed by necrosis of epithelium and formation of numerous superficial ulcers of the trachea and bronchi. When the process extends into the small bronchioles, their lumina become blocked by necrotic epithelium, inspissated mucus and leukocytes, resulting in atelectasis of many of the primary lobules. Thickening of the walls of bronchioles is due to

*This term has been applied to lesions varying from simple purulent bronchitis and bronchopneumonia, with its concomitant distention with fluid and cells of the peribronchial lymph spaces, to postpneumonic atelectasis of primary lobules, following the obstruction of bronchioles and thickening of alveolar walls due to increased number of septal cells. It seems desirable to avoid extensive use of the term until the process is better understood and more clearly defined.

hyperemia, edema, and infiltration of mononuclear cells. Thickening of alveolar walls immediately adjacent to the bronchioles is brought about by dilatation of capillaries and increase in number of alveolar phagocytes. Polymorphonuclear leukocytes are few except in the lumen of bronchioles which contain necrotic epithelial cells.

The alveolar spaces contain edema fluid and cells, chiefly of the mononuclear varieties, and very little fibrin. During severe epidemics, fatal cases may show more extensive areas of consolidation with hemorrhage, similar to the experimental disease in ferrets and mice. Hyaline membranes closely adherent to the walls of dilated alveolar ducts and resembling condensations of hyalinized fibrin have been observed in many cases of influenza. The membranes do not give the characteristic staining reaction of fibrin. Besides occurring in other viral infections (Fig. 538) and in bacterial pneumonia following influenza,^{48, 49} similar hyaline membranes are found in the lungs of those killed by war gases and often in the lungs of newborn babies, asphyxiated by the aspiration of amniotic fluid.

With the invasion by bacteria of the denuded areas of the mucosa, the sputum changes from a tenacious, sticky gray or near-white mucus, to yellow, sometimes blood-streaked, mucopurulent exudate. The victim may have difficulty in clearing his bronchi of secretion and exudate because of the extensive destruction of ciliated epithelium. With the retention of exudate, the danger of secondary pneumonia from aspiration is greatly increased. The characteristics of the exudative consolidation of the parenchyma are determined by the nature of the bacteria principally responsible for the second phase of the infection and will be discussed under the headings of streptococcal pneumonia, pneumococcal pneumonia, etc. (See also page 324.)

Measles.—In this common disease of childhood, as in influenza, it is difficult to dissociate the lesions produced by the virus from those produced by secondary invaders. In this case, hemolytic streptococci are commonly present in severe and fatal cases as the predominant invader or in pure culture (see also page 330).

Ornithosis; Psittacosis.—This respiratory infection is usually acquired by the close association with infected birds or by the inhalation of dust from their droppings. Most of the cases have been traced to parrots, parakeets, and other members of the psittacine family, hence the name psittacosis. It is now known that many other birds not of the parrot family such as canaries, pigeons, doves, and chickens can harbor the virus and are capable of transmitting the disease to human beings. The more inclusive term "ornithosis" is therefore preferable to the earlier term "psittacosis" (see also page 325). Smadel⁵⁰ estimated that one-fourth of sporadic cases of atypical pneumonia were due to infection by the virus of psittacosis (ornithosis).

Q Fever.—Atypical pneumonia occurs in the more severe infections of the Q fever type, especially in the cases which have been identified in America (see also page 306).

PNEUMONIAS AND GRANULOMAS OF UNKNOWN ETIOLOGY

Primary Atypical Pneumonitis.—A poorly defined symptom complex appearing very commonly in adolescents and young adults, characterized by a slow, insidious onset and relatively mild symptoms, has been observed with great frequency in various parts of the United States, Europe, and elsewhere, and described under various names such as "primary atypical pneumonia," "virus pneumonia" (since no bacterial etiology has been discovered), and "bronchopneumonia of unknown etiology; variety X."⁵¹ Clinically and pathologically similar are some of the cases of psittacosis and Q fever which have been described. Deaths are rare. In the few cases studied post mortem, the principal lesions have been confined to the lungs but the details of the lesions described have not been uniform. Sometimes there is firm dark-red consolidation. Bronchioles are thickened and contain mucus, leukocytes, and degenerated epithelial cells. The alveolar exudate consists of edema fluid, erythrocytes, monocytes, lymphocytes, plasma cells, and a few neutrophiles (Fig. 538). Massive exudation is usually associated with secondary bacterial invasion. There is a pronounced tendency for organization of exudate to occur, with the result that the parenchyma undergoes extensive diffuse or patchy fibrosis. (See also page 326.)

Acute Diffuse Interstitial Fibrosis.—Hamman and Rich⁵² have described cases of acute pulmonary disease in which diffuse fibrosis was observed to be present at autopsy in prominent degree as early as thirty-one days after the onset of symptoms. Pathologically these were characterized in the early stage by acute exudative pneumonitis in which hyaline membranes were prominent, neutrophiles and monocytes relatively few; later, monocytes, fibroblasts and a scattering of eosinophiles appeared. Invasion of the hyaline membranes by fibroblasts resulted in great thickening of the alveolar walls and the appearance of "interstitial fibrosis" (Fig. 539).

The writer has seen similar cases in which interstitial and intra-alveolar fibrosis occurred diffusely through the lungs after intervals of three weeks to three months following attacks of acute febrile pulmonary disease. One of these showed polyoid masses of fibroblasts in many of the bronchiolar lumina as well as plugs of organized exudate in the alveoli (Fig. 540).

Kneeland and Smetana⁵² described a case among a group of bronchopneumonias of un-

usual character and underdetermined etiology which anatomically resembled those later studied by Hamman and Rich. The present tendency is to consider these cases as probably of viral etiology since bacteria are not constantly obtainable in significant numbers by the usual methods.

Viral Pneumonia in Infants.—The evidence which links several different kinds of pulmonary lesions in infants with a viral etiology is presumptive only and based upon the finding of intranuclear and intracytoplasmic inclusions in the epithelial cells of the lining of the bronchioles and sometimes in the cells of the alveolar walls. In some of the cases, the destructive effects upon bronchiolar epithelium and the formation of multinucleated giant cells resemble similar effects observed in known viral

furnished. Pinkerton, Smiley, and Anderson⁵⁷ have called attention to the similarities between giant cell pneumonia of infants and distemper pneumonitis of minks and other species. Nineteen of the twenty-seven cases reported by Hecht⁵⁸ were pneumonias complicating measles. The frequency with which the giant cell picture occurs in association with measles suggests an etiological relationship, but not all of the reported cases have manifested clinically recognizable measles. Denton,⁵⁹ in his description of the findings in fatal cases during a severe epidemic of measles in 1925, stressed the frequency with which giant cells were found in the lungs.

Pulmonary Lesions in Rheumatic Fever (Rheumatic Pneumonitis).—The observation that some form of acute disease of the lungs

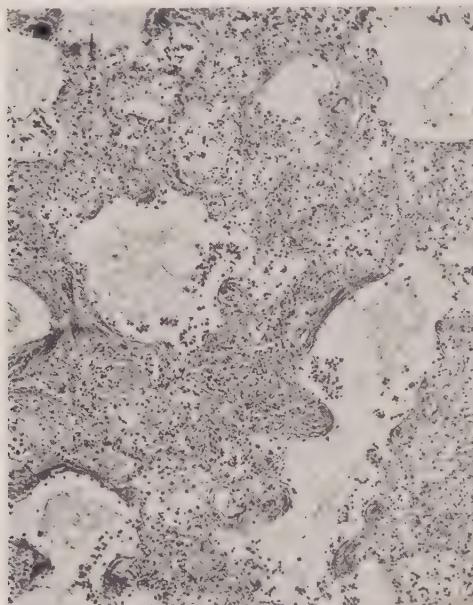


Fig. 538.

Fig. 538.—Viral pneumonitis showing hyaline membranes, leukocytic and fibrinous exudate in alveoli. Death two weeks after onset.

Fig. 539.—Acute diffuse interstitial fibrosis of the lungs. (Section by courtesy of Dr. A. R. Rich.)

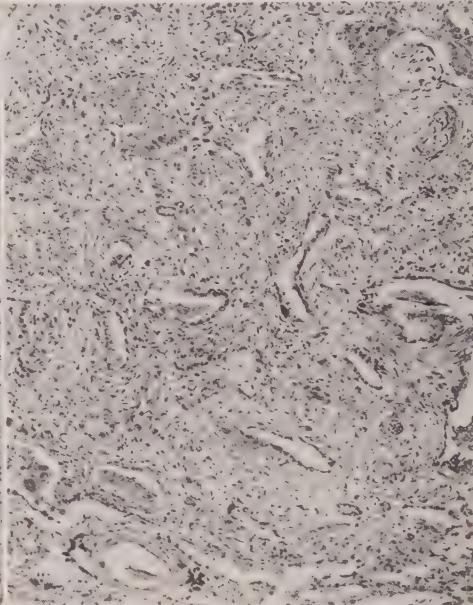


Fig. 539.

diseases of man and animals. Various histologic pictures have been described. Some are characterized by the presence of intranuclear inclusions only,⁵⁴ some by cytoplasmic inclusions,⁵⁵ and one group of cases is characterized by the presence of large multinuclear giant cells,⁵⁶ with both intranuclear and intracytoplasmic inclusions in epithelial and alveolar cells⁵⁷ (see also page 326).

All of these have in common a subacute or chronic course, injury to the epithelial lining of bronchioles and "interstitial pneumonia." While so far no filtrable agents have been isolated and identified, the evidence seems sufficiently sound to permit its acceptance as a working basis until more certain proof is

and pleura occurred frequently during the acute phases of rheumatic fever has been recorded in the clinical literature for more than a century but it was not until about twenty-five years ago that accurate histologic descriptions of the characteristic pulmonary lesions were published.^{59, 60} In clinical and pathological interpretation it is difficult to dissociate the effects of passive congestion from those of inflammatory responses, especially in cases presenting advanced mitral stenosis; consequently the characteristic lesions are recognized most clearly in those cases in which death occurs during the acute stages of the disease, before the development of advanced cardiac damage. Such cases are often seen in the Rocky Mountain area

and North Atlantic states where the incidence of rheumatic fever is especially high (see pages 451 and 459).

Roentgenographic findings are those of increased prominence of hilar markings and widespread, poorly-defined densities, often sparing the basal portions of the lungs, and with a tendency to clear in one area while reappearing in another, much as in primary atypical pneumonitis.⁶¹ The lesions are nonsegmental and readily differentiated from the shadows produced by infarcts. Sometimes the densities of inflammatory infiltrates are masked by the diffuse density of edema of both lungs.

contrast with the homogeneous dark red appearance of passive congestion, some of the firmer masses of tissue are as pale as normal parenchyma on sectional surfaces. In active lesions the smooth dry surfaces are dotted with small hemorrhages.

The microscopic picture of the early phase of the inflammatory response is not specific but most closely resembles that of some of the viral pneumonias, with irregular engorgement of capillary blood vessels, swelling and separation of the septal cells, edema, scanty fibrin, and the formation of hyaline membranes (Fig. 542). These are readily distinguished from

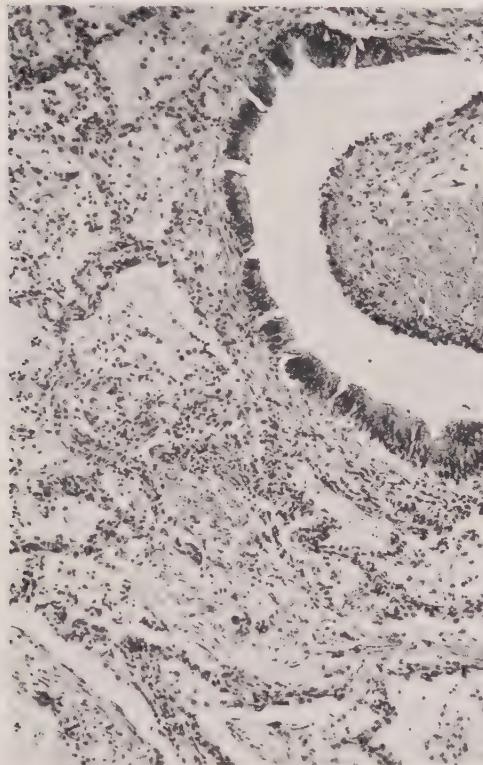


Fig. 540.

Fig. 540.—Atypical pneumonitis. Organization of exudate in alveoli and partly organized polypoid plug of exudate in bronchiolar lumen.

Fig. 541.—Organized infarct of lung. Streamers of fibrocytes pass through interalveolar pores from one alveolus to another.

While the gross appearance of the lungs at necropsy is not distinctive, there are certain features which tend to distinguish the inflammatory lesions of pneumonitis from the effects of vascular stasis. Instead of the wet, spongy or doughy consistency of passive congestion with edema, portions of the lungs are elastic and tend to retain their shape. In cases coming to autopsy after repeated attacks of fever, fibrous pleural adhesions in random distribution usually will be found. Areas of fibrous pleural thickening merge with areas of dullness where films of fibrin adhere to the pleura. In striking

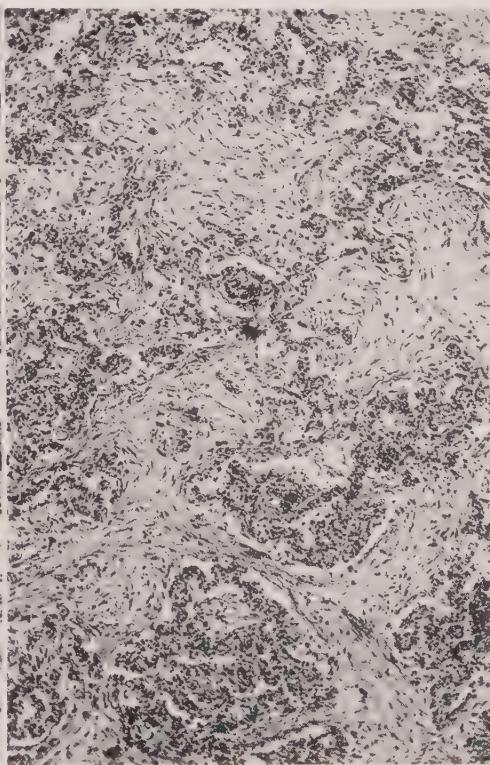


Fig. 541.

fibrin by specific staining reactions and appear to be formed largely by the fusion and degeneration of masses of free septal cells which constitute the major component of the exudate. Neutrophilic leukocytes are scanty. Monocytes, lymphocytes, and plasma cells are seen in small foci within the areolar tissue which surrounds small blood vessels. Following the early exudative and proliferative stage, just as in the heart and serous membranes, the pulmonary lesions become less diffuse and more focal. Nodules of pleomorphic histiocytes and fibroblasts intermingled with various proportions of

lymphocytes and plasma cells are formed within the alveolar septa and protrude into air sacs, apparently replacing masses of fibrinocellular exudate.⁶²⁻⁶⁴ Similar cellular masses are seen also in the perivascular connective tissue. Multinuclear giant cells, resembling those derived by atypical nuclear proliferation of septal cells, are found in the granulomatous foci and free in the alveolar spaces. While isolated cells

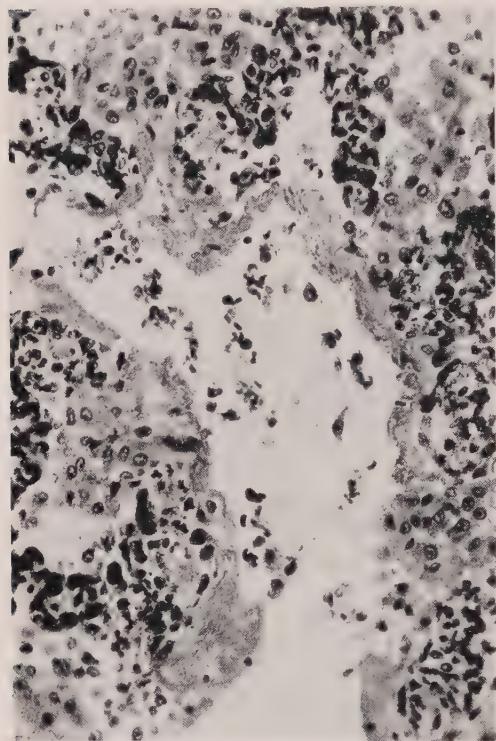


Fig. 542.—Rheumatic pneumonitis, early stage. Masses of large mononuclear cells merge with thick membranes of amorphous substance ("hyaline membranes"), occupying much of the air space.

and those constituting the granulomatous foci often resemble the atypical histiocytes of myocardial Aschoff bodies, their loose arrangement, lack of polarity, and random distribution in the pulmonary parenchyma do not conform very closely to the usual conception of Aschoff bodies. Alterations in the blood vessels are inconspicuous in the early phase of evolution of the lesions but they gradually become more so as a result of hyaline thrombosis of capillaries and of proliferation of endothelium and cellular infiltration of the adventitia of the larger vessels. The arterial lesions are not nodular as they are in polyarteritis nodosa. Of greatest importance in comprehending the mechanism of the pulmonary arterial hypertension and later development of right ventricular hypertrophy is the residual diffuse fibrosis of the lung following organization of exudates. In the conception developed by Gouley⁶⁵ the pulmonary

vascular bed is permanently constricted by diffuse fibrosis of alveolar septa and by diffuse sclerosis of arterioles and small arteries. The resulting pulmonary arterial hypertension and right heart strain may outweigh in importance the effects of valvular deformities.

Uremic Changes in the Lung.—In addition to the widespread hemorrhages of mucous and serous membranes, fibrinous pericarditis, necrosis and ulceration of intestinal mucosa, cerebral edema and the characteristic alterations of the pancreas, the lungs of patients in whom there are clinical and biochemical manifestations of uremia (see page 561) often show mottled densities in x-ray films. These are most often the result of simple hemorrhage and edema of the parenchyma but in some cases fibrin is abundant, and inflammatory cells of all types make up an exudate which justifies the use of the term "uremic pneumonitis." Pulmonary congestion and edema as a result of cardiac failure are often present but not invariably so. In the absence of bacteria, one is forced to the interpretation that the exudation is the result of focal alterations of capillary permeability, associated with azotemia. Thickening of alveolar walls, fibrinous alveolitis and hyalinization of exudate in the form of plugs and membranes in the later stages, are followed by various degrees of fibrous organization of exudate.⁶⁶⁻⁶⁸ Lesions of different ages, varying from fresh fibrino-hemorrhagic exudate to advanced fibrosis, are found occasionally in cases of prolonged or recurring uremia.

Sarcoidosis (Besnier-Boeck-Schaumann's Disease).—The lesions of this generalized granulomatous disease occur most frequently in lungs, spleen, lymph nodes, and skin but have been observed in practically all tissues and organs of the body, including the central nervous system.⁶⁹⁻⁷⁴ Because of their close similarity to



Fig. 543.—Roentgenogram of chest in pulmonary sarcoidosis. "Soft" densities are widely scattered through both lungs.

the proliferative, noncaseating nodules of tuberculosis, i.e., epithelioid cell tubercles, the differentiation of the two is often difficult and sometimes impossible.

PATHOLOGICAL ANATOMY.—Since in the majority of cases, respiratory symptoms are absent or mild⁷⁴ the first evidence of pulmonary lesions is usually discovered by roentgenography⁷⁵ (Fig. 543). The pattern varies from widely disseminated miliary lesions to bulky, coalescent masses in one or both lungs and with a predilection for the middle and basal portions of the lungs. Those cases which exhibit massive enlargement of the hilar and mediastinal lymph nodes are easily mistaken for Hodgkin's disease or lymphosarcoma. In some cases, the extent of involvement is limited to small areas. These tend to be distributed in the pleura and subpleural parenchyma, in the peribronchial parenchyma and in the alveolar septa.⁷⁶ Clinical and roentgenographic evidence suggests that spontaneous "resolution" of the lesions may take place over a long period of time. In the lung examined after death, the lesions are characteristically pearly gray, discrete or confluent, and free from gross evidence of necrosis.

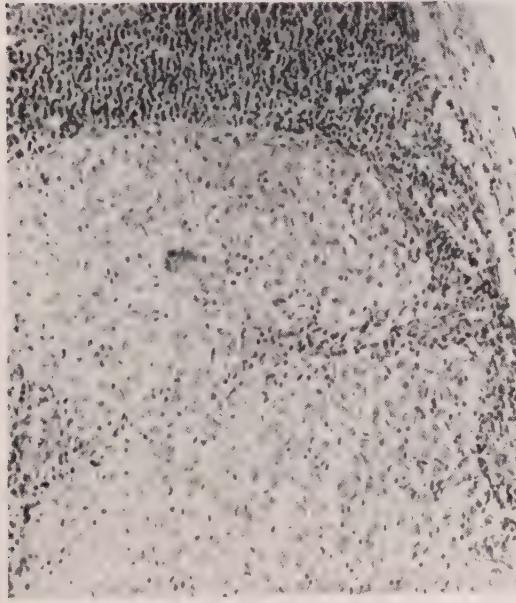


Fig. 544.—Subpleural epithelioid cell masses in sarcoidosis.

The unit lesions consist of discrete nodules of epithelioid histiocytes, similar to those of tuberculosis, leprosy, berylliosis (page 664) and several other granulomas (Fig. 544). They often contain multinucleated giant cells of the foreign body type which generally differ from the Langhans giant cells of tuberculosis in their greater size and larger number and random distribution of nuclei. Slight central necrosis is often seen but caseation is not a common feature of the lesions. In those cases in which caseation has been described, it is not clear

that an associated tuberculosis had been definitely excluded. At the margins of the nodules, lymphocytes may be scanty or absent, in contrast with the typical nodules of tuberculosis which characteristically are surrounded by dense zones of lymphocytes. This feature, however, is not a reliable criterion for the histologic differentiation of these two diseases. As in tuberculosis, the unit lesions tend to appear in clusters and by partial coalescence to form conglomerate masses but, unlike tuberculosis, they do not completely fuse to form large necrotic encapsulated tubercles.

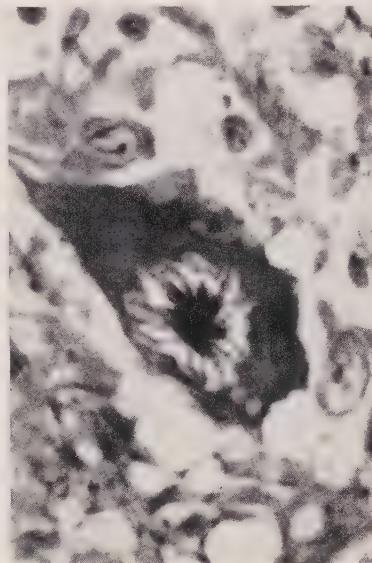


Fig. 545.—Stellate inclusion in giant cell.

The involution of lesions is brought about by the transformation of histiocytes into fibroblasts (or their replacement by fibroblasts) at the periphery of the unit nodules. When involution is complete the entire epithelioid nodule is replaced by fibrous tissue. The giant cells tend to persist until the last stage of fibrous replacement.

Star-shaped acidophilic bodies, referred to as asteroids, and spherical or ovoid basophilic bodies are found infrequently within the giant cells or partly extruded from the large vacuoles of their cytoplasm. The basophilic bodies often show concentric lamination, may show yeastlike budding and are nearly always calcified.⁷⁶ There is some morphologic evidence that they may represent the late calcifying stages of asteroids.

ETIOLOGY AND PATHOGENESIS.—The earliest accounts of this disease were confined to the lesions of the skin of the fingers, face, and ears and to enlarged superficial lymph nodes.⁶⁹ In 1899, Boeck⁷⁷ first described the histologic appearance of cutaneous lesions and introduced the term "multiple benign sarcoid." Later (1904) the lesions of the bones of fingers and toes were recognized as a part of the same

disease⁷⁸ and, still later, widespread visceral lesions including those of the lungs were described.^{79, 80} The belief held by many that sarcoidosis is in some way related to tuberculosis is based upon the histologic similarity of its lesions to epithelioid cell tubercles and to the fact that, in some of the patients, recognizable tuberculosis is the cause of death. Against this view are the observations that clinical tuberculosis is present in only a small proportion of patients, positive tuberculin reactions are no more frequent than in the general population,⁸¹ and complement fixing antibodies show a low incidence and low titers. When inoculated with avirulent tubercle bacilli (BCG) the majority of patients continue to exhibit anergy to tuberculin but develop complement fixing antibodies as do normal controls.⁸²

Hodgkin's Granuloma.—The lungs are involved in more than one-half of cases of lymphogranulomatosis and, according to the observations of Verse,⁸³ in about 10 per cent of these the lesions appear to arise primarily in the pulmonary parenchyma, extending secondarily to bronchopulmonary and mediastinal lymph nodes. In two cases which the writer has studied, the extent of involvement of lymph nodes by comparison with that of the lung was relatively slight. Moolten⁸⁴ has described such cases and stressed the inflammatory exudative nature of the lesions in their early stage of development. Such observations suggest that in a considerable number of cases the respiratory system may be the portal of entry of an unknown infective agent and that the broncho-



Fig. 546.

Fig. 546.—Hodgkin's disease. Necrotizing bronchiolitis.

Fig. 547.—Hodgkin's disease. Specific granulomatous tissue projecting into lumen of small bronchus.



Fig. 547.

pulmonary and mediastinal lymph nodes are involved secondarily.

At first the reaction is nonspecific, consisting of catarrhal bronchiolitis and alveolitis. Fibrin, leukocytes, plasma cells, and large mononuclear phagocytes fill the air spaces. The exudate undergoes organization by specific granulomatous tissue and by nonspecific fibrous tissue. Thickening of alveolar walls takes place as in tuberculosis and in actinomycosis, due in part to obliteration of air spaces by ingrowth of granulomatous tissue and organization of exudate. The intrapulmonary nodules of lymphoid

While the etiology must be considered as completely unknown, evidence is accumulating that the respiratory tract is more consistently involved than any other functional system, suggesting that the unknown bacterium, virus, or other agent may enter by this route, later to become generalized by lymph and blood stream to form secondary foci in lymph nodes, spleen, bone marrow, liver, skin, eyes, and other less commonly involved tissues. The localization of lesions is strikingly similar to that of tuberculosis and other infectious granulomas.

tissue are converted into granulomatous masses which exhibit the characteristic mixtures of cells, swollen histiocytes, Sternberg-Reed giant cells, plasma cells, polymorphonuclear neutrophiles and eosinophiles and, in the late stage, dense masses of fibrous tissue.

The gross form varies greatly from one case to another. In the widely disseminated form, the lesions take on the character of a granulomatous bronchopneumonia. The foci are gray, firm, and dry, with poorly defined borders, and vary widely in size and shape. The scars are linear or fan-shaped in the parenchyma, never appearing as discrete nodules as in silicosis or tuberculosis.

In the form with bulky granulomatous enlargement of the mediastinal lymph nodes, the lungs appear to be invaded secondarily by tumorlike masses of infiltrates, extending peripherally along bronchi or blood vessels from the hilum and by direct extension through the capsules of the nodes.^{85, 86}

SPECIFIC BACTERIAL INFECTIONS OF THE LUNGS

Of the two most important bacterial infections of the lung, pneumococcal pneumonia furnishes the best and most closely studied example of the acute inflammatory responses to bacterial invasion. For this reason and not solely because of its clinical importance, it is discussed in much greater detail in the following pages than are the other acute bacterial infections of the lung.

The second, tuberculosis, is the subject of a separate chapter (page 234).

Syphilis has a relatively slight tendency to pulmonary localization and its importance is dependent mainly upon the peculiar consolidation, "pneumonia alba," of the syphilitic stillborn. Gumma of the parenchyma and specific arteritis of the pulmonary vessels are among the rarities.

Pneumococcal Pneumonia

Inflammation of the lung, when caused by one of the more virulent types of pneumococci and not preceded by a major episode of bronchial inflammation of viral or chemotoxic etiology or by circulatory disturbances in the lung as in heart failure, is considered to be a primary pneumonia. As a rule, primary pneumococcal pneumonia begins abruptly, affects at its onset only a limited area within one lobe and spreads diffusely through the air spaces to involve an entire lobe. Other lobes may be involved by intrabronchial "metastasis" or by

direct extension to adjoining tissue in the hilar region where an interlobar septum is deficient. This is so characteristic of pulmonary infections by pneumococci that we consider the term "lobar pneumonia" and "pneumococcal pneumonia" as practically synonymous. The few exceptions are associated with infection by Friedländer's bacilli and streptococci which occasionally are found in preponderance in the lobar form.

With the latter organisms, however, there is a greater frequency of multifocal infections, and therefore two or more lobes may be found to contain multiple lesions in approximately the same stage of development. This is the lobular form. With the more virulent strains of pneumococci, particularly of types I, II, and III, multifocal lesions rapidly extend to become coalescent, and, after a few days, it may be difficult to determine whether the infection began as a unilobular or as a multilobular process. The form is of little practical importance. The virulence of the pneumococcus and the extent of the lesions are of prime importance.

Types and Virulence of Pneumococci.—Pneumococci vary greatly in their ability to produce disease, and the differences are determined in large measure by their type. The pneumococci are considered on page 206.

Accessory Factors in Etiology.—Although, at present, the available evidence indicates that the more virulent strains of pneumococci can initiate progressive inflammatory processes in the lung if they reach the parenchyma in sufficiently great numbers, it is clear that such infections are often precipitated by the presence of certain conditions which have in common: (1) edema of the pulmonary parenchyma, (2) increased mucoseroous secretion in the respiratory tract, and (3) enhanced opportunity for aspiration of bacteria, mixed with secretions. Events often followed by pneumonia are: chilling of the body from exposure, particularly after wetting of the clothing (pulmonary edema); traumatic injury of the chest (pulmonary hemorrhage and edema); ether anesthesia (pulmonary edema and opportunity for aspiration of bronchial secretions); alcoholic intoxication (exposure, pulmonary edema, aspiration of secretions while in state of coma); cardiac failure with pulmonary edema; and viral infections, especially coryza and influenza.

The role of viruses as an accessory factor in the development of bacterial pneumonia is by no means settled. The demonstration by Shope⁸⁷ of the complementary or synergistic action of a virus and bacillus (*Hemophilus suis*) in the causation of swine influenza reopens the question of the possible role of viruses in the so-called primary pneumococcal pneumonias as well as in those already recognized as secondary

pneumococcal bronchopneumonias. In the pandemic of influenza of 1918-1919, many of the cases of pneumococcal pneumonia were of the lobar or so-called primary form.

Experimental evidence has been furnished in support of the idea that some of the predisposing conditions exert their effects by interfering with the closure of the epiglottis which under normal circumstances prevents the aspiration of large quantities of mucus, saliva, or foreign bodies. Nungester and Klepser⁸⁸ have demonstrated that in ether anesthesia, alcoholic intoxication, or the sudden immersion of the body in cold water, the epiglottic reflex is inhibited and the unclosed glottis allows liquids to be aspirated from the mouth and pharynx. Previous evidence was submitted by the same workers that mucin has a protective effect upon bacteria in the tissues and body cavities, preventing immediate phagocytosis and permitting free proliferation during the period of incubation of the infection. Starch paste, such as that used by Robertson⁸⁹ for the induction of experimental pneumonia in dogs, probably acts in a slightly different manner. The starch itself is an irritant producing inflammatory edema in the parenchyma and thus offering both a suitable culture medium for the injected pneumococci and a protection from phagocytes since the latter do not act efficiently in a fluid medium.

Route of Infection.—With very rare exceptions, pneumococci reach the parenchyma of the lung through the bronchi. Since the flow of lymph is always from the parenchyma toward the hilum, the theory that an infection may arise in lymphoid tissue of bronchial mucosa or lymph nodes and spread peripherally into the parenchyma can be dismissed from consideration. Initiation of an acute diffuse inflammatory process by the arrest of bacterial emboli in the pulmonary vessels is not an impossibility but apparently does not occur very often in pneumococcal infections although it is a common occurrence in staphylococcal and streptococcal infections. An occasional case of pneumococcal otitis media or valvulitis of the right side of the heart may give rise to secondary infection of the lung but rarely to typical lobar pneumonia.

The intact healthy bronchial mucosa is highly resistant to infection by pneumococci, but when virulent cocci in sufficient numbers reach the respiratory bronchioles and alveoli, acute inflammation with edema invariably results. The course is shortened by previous immunization, but complete immunity is never attained. In nonimmune susceptible subjects, extremely small quantities of bac-

teria are sufficient to initiate the process. It is possible that a few hundred pneumococci or even fewer may sometimes reach the lung in droplets carried by the air stream. More probably, larger quantities of mucoserous secretion from pharynx or nose are aspirated into the larynx and trachea, reaching the finer bronchial rami through the force of gravity, and driven beyond the terminal bronchioles by deep inspiratory movements incidental to unusual exertion, coughing, sneezing, or accidents of deglutition. By this method, relatively large quantities of bacilli-laden fluid may reach the parenchyma at one time. It is difficult to explain otherwise why pneumococcal pneumonia so regularly arises in a limited portion of one lobe rather than as multiple foci in both lungs as one should expect if such infections were the result of inhalation of minute droplets, carried in the air stream.

Mode of Development of the Lesion.—The development of pneumococcal pneumonia is best understood by comparing it, step by step, with acute inflammation in a vascular areolar tissue. When it is fully realized that alveolar walls are not imperforate sacs capable of confining the exudate, it can be appreciated that the similarities to connective tissue structures are greater than the differences. The earliest observable response to the presence of pneumococci in both consists of local hyperemia, edema, mobilization of macrophages (septal cells in the lung), and migration of leukocytes into the area. This response is mild at first and, if the bacteria are destroyed by the mobilized macrophages within a few hours, no further extension of the process may take place. This outcome is possible if the virulence of the cocci is low, the dose is small, or if specific immunity exists. With failure of prompt destruction of the pneumococci, rapid proliferation takes place in the liquid exudate. The edema fluid, lacking specific immune globulins and containing only a few phagocytes, furnishes a medium in which they can multiply at a rapid rate, and in a few hours their numbers are far in excess of those which can be destroyed by the more gradually increasing numbers of leukocytes. As the numbers of bacteria increase, there is an enhancement of the

intensity of the inflammatory response. Edema fluid, loaded with pneumococci, flows through the openings in the alveolar walls and through the lumina of alveolar ducts and bronchioles into other lobules in an ever widening area. The direction of spread is determined by gravity and by respiratory movements. The rapidity of extension of exudate is determined by the rate of increase of cocci and not, as assumed by some writers, due to the intensification of hypersensitivity. Meanwhile, the exudate in the oldest part of the focus becomes denser, fluid is replaced by leukocytes, and the precipitated fibrin gradually becomes more abundant.⁹⁰

prehension of the process can be obtained by considering the histologic alterations as phases of a continuous dynamic process which reaches its climax with the complete filling of the air spaces with fibrin and leukocytes, and then gradually subsides. Since the process as a whole is a rapidly expanding one, continuously involving new areas of tissue, the stage of the exudative cycle will vary from one area to the next, depending upon the time of involvement. While consolidated tissue in one part of a lobe is showing a late stage of the cycle, another part will be passing through the initial stage. For purposes of description it is convenient to divide the process into three or four



Fig. 548.

Fig. 548. Empyema in case of pneumococcal lobar pneumonia.

Fig. 549.—Lobar pneumonia in late fibrinous stage (gray hepatization). Complete consolidation of lower lobe; atelectasis of upper lobe. Interlobar fibrinous pleurisy.



Fig. 549.

Stages of Pneumonia.—Following the classical description of Laennec, it has become customary to subdivide the pneumatic process into four stages, based upon color and consistency of the tissue with its contained exudate. A better com-

phases and to correlate the microscopic appearance of a limited area or zone with its gross appearance. These are best studied in experimental animals, sacrificed at different periods after inoculation, or in human lungs after death

by comparing the condition of the oldest part of the lesion with each successive zone of more recent development, outward to the advancing edema zone.

STAGE 1.—Stage of inflammatory edema. In the site of origin of pneumococcal pneumonia, this phase is rarely seen in the human lung. In advanced consolidation it is represented by an irregular zone at the advancing margin of the exudate.

truding into the alveolar spaces or floating free in the edema fluid. A few neutrophilic leukocytes have reached the spaces, but many more have accumulated in the capillaries and are found in the process of migrating through the walls of the engorged capillaries. The fluid exudate is teeming with bacteria which can be demonstrated readily in suitably stained sections or smears. If the process

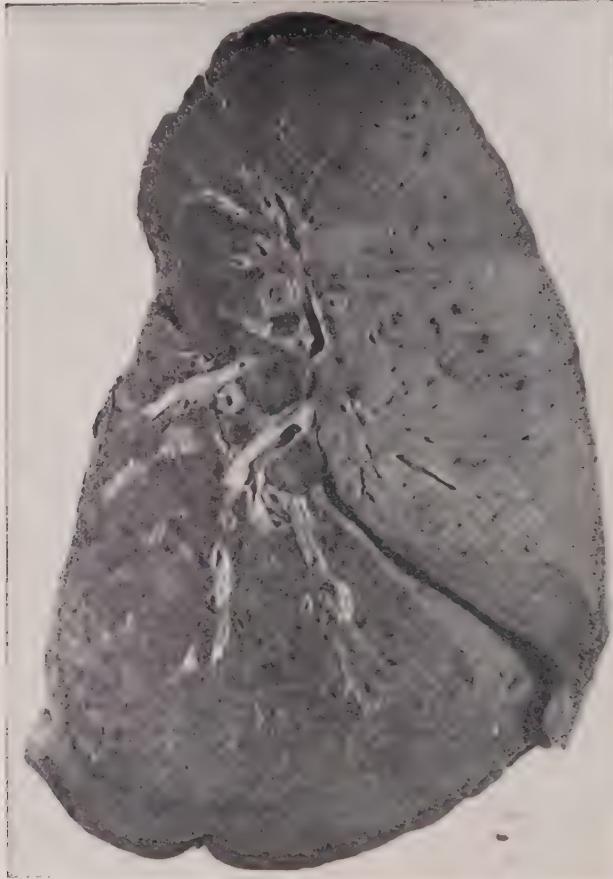


Fig. 550.—Lobar pneumonia. Late gray hepatization of dorsal part of upper lobe (middle one-third to the right of figure); early hepatization (in triangle above); edema stage in apical portion; hyperemia of lower lobe.

It is dull gray-red and translucent, intermediate in depth of color and consistency between the deep red of the collapsible, unconsolidated but hyperemic tissue and the pale red of early consolidation. The fluid can be expressed readily from the parenchyma. Microscopic sections from this edema zone show dilatation and increased tortuosity of the alveolar capillaries. The septal cells are rounded, pro-

is arrested or slowed by chemotherapy or by mobilization of humoral antibodies and phagocytes, the edema zone disappears and the transition between hyperemic, comparatively dry lung and consolidated tissue is abrupt. As soon as the edema fluid becomes abundant, but not before, the perivascular and peri-bronchial lymph spaces become distended with fluid and the hilar lymph nodes

begin to swell with fluid. A few phagocytized pneumococci can be found in leukocytes and macrophages in the lymph channels and in the peripheral sinuses of the lymph nodes, but they are much fewer here than in the alveolar exudate.

duced lesions, may replace the fluid with solid masses of cells within eighteen hours⁹¹ from the time of injection of pneumococci. A delicate net of fibrin is present at this time but cannot be seen in the areas of solidly packed cells. In

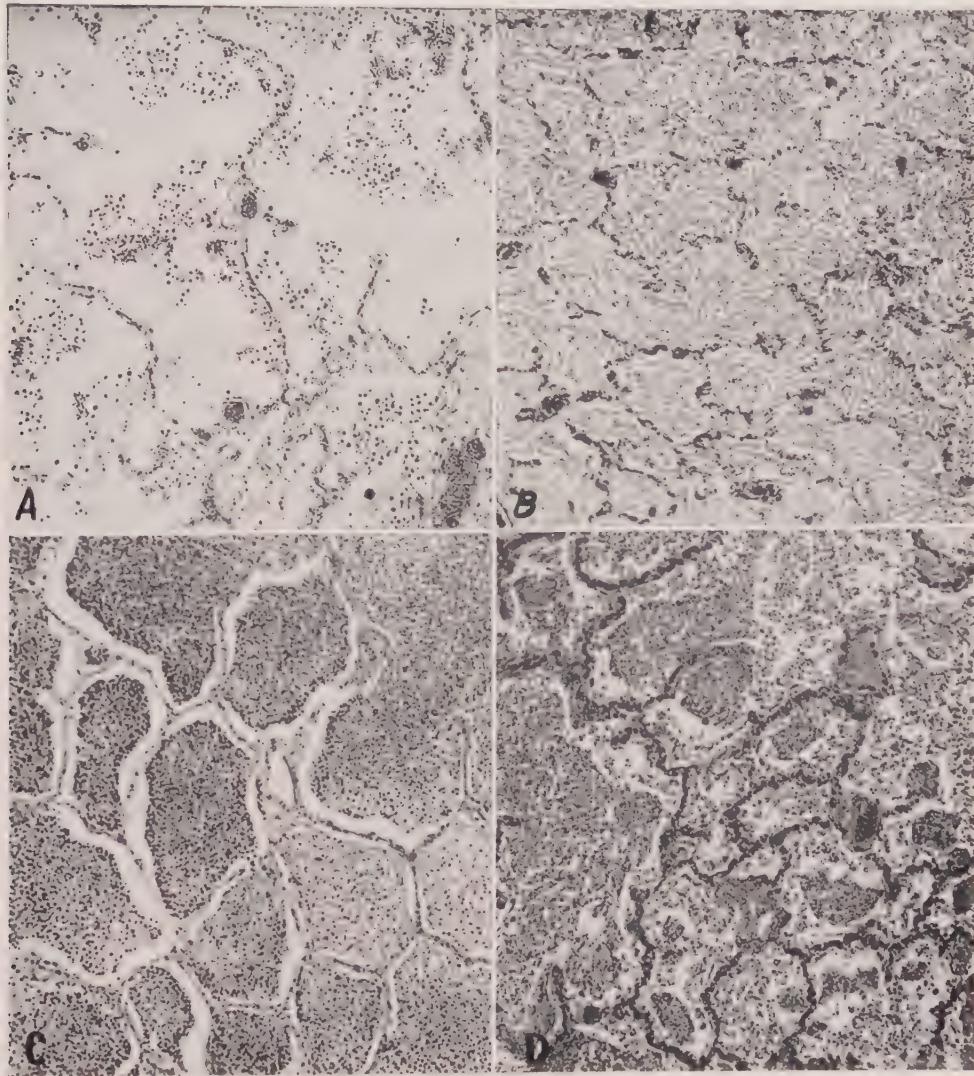


Fig. 551.—Stages of lobar pneumonia. *A*, Edema and early leukocytic infiltration. *B*, Leukocytic stage; engorgement persists; fibrin is scanty. *C*, Late fibrinous stage; beginning of contraction of the alveolar exudate. Alveolar walls are ischemic. *D*, Resolution. Macrophages predominate. Masses of fibrin lie free in the alveolar spaces and alveolar capillaries are engorged.

STAGE 2.—Stage of leukocytic exudate. Early hepatization. The migration of leukocytes, predominantly polymorphonuclear neutrophiles, into the inflamed areas is rapid and, in experimentally pro-

the alveoli of human lungs a weblike reticulum of fibrin can be observed frequently in the latter part of the edema stage, before the leukocytes have become numerous. At this time also, erythro-

cytes in small numbers are found in the air spaces with leukocytes, fibrin, and edema fluid. They vary greatly in number from place to place and from one case to another. Experimental evidence indicates that the amount of intra-alveolar hemorrhage varies with the intensity of the inflammatory process. It is slight in mild infections, and massive in overwhelming infections due to highly virulent pneumococci.

With the replacement of fluid by more solid exudate, the alveolar capillaries become less conspicuous and the alveolar walls appear thinner. In the ordinary section stained with hematoxylin and eosin, the septa are difficult to distinguish in the solid mass of leukocytic exudate. Compression is, in part, responsible for the diminished size of capillaries, but thrombosis also plays some part in the diminished flow of blood through the vessels. The effects of both factors become intensified in the succeeding stage.

The gross appearance of the leukocytic stage varies more than that of any other. The tissue is airless, moist, and fairly firm, but not so firm as in the next part of the cycle when fibrin reaches its maximum. The color is sometimes deep dull red, and for this reason commonly designated as the stage of "red hepatization" but more often light red to yellowish-pink. The redness is due to the persistence of capillary engorgement. Only exceptionally are there sufficient numbers of erythrocytes in the alveolar spaces to produce a deep red color. The yellowish cast is imparted by the mass of leukocytes as in the buffy zone of sedimented blood. Ordinarily, the second stage is represented by a narrow, poorly defined, irregular zone between the firmly consolidated tissue and the advancing edema zone. It is, therefore, a stage of only a few or several hours' duration and is never uniform throughout an entire lobe.

STAGE 3.—Fibrinous stage. Hepatization. The deposition of fibrin is continuous, beginning with the first outpouring of fluid and continuing as long as exudation continues. Since fibrin is relatively insoluble in the tissues, it increases progressively in quantity and density while fluid is draining away through the lymphatics and while leukocytes are dying and disintegrating. According to

Loescheke,⁹² surviving leukocytes may migrate from an area in which bacteria have disappeared to areas in which they are still numerous, in this way further depleting the exudate of cells. Thus, at the climax, fibrin has reached its maximum, pneumococci have been destroyed by phagocytes, and leukocytes have begun to disappear from the area. The threads of fibrin became coarsened and separate from the alveolar walls. Skeins of coarse fibrinous threads can be seen to pass through the pores of Kohn from one alveolus to another. With the contraction of fibrin, the pressure previously exerted by the intra-alveolar exudate is relaxed and those capillaries not obstructed by thrombi become re-expanded and filled with flowing blood.

This stage is much more prolonged than the first two. Frequently that part of a completely consolidated lobe which was first to be involved remains in the fibrinous stage until the portion last to be involved has passed through the first two transient phases to reach the stage of true hepatization. Because of the relatively long duration of the fibrinous phase, an entirely consolidated lobe, having reached this stage, may be found to be uniform in color and consistency throughout. The dominant color on sectional surface is gray, imparted by the fibrin, but within the lobe there is often a mottling of the gray surface by pale pink areas and by areas more yellow than gray, due to predominance of leukocytes. The firmness of the tissue in this stage is comparable with that of normal liver, hence the term "gray hepatization" which describes it with fair accuracy and accounts for the frequency with which medical students mistake the appearance of lobar pneumonia for that of a discolored liver.

On the pleural surface, the impressions of the ribs are readily visible, for the pneumonic lung completely fills the thoracic cavity and has lost its elasticity because filled with noncompressible exudate. Its volume is the same or slightly smaller than that of the fully expanded normal lung. The pleural surface over the involved area is ordinarily dull and finely granular, due to the presence of a film of fibrin. In the earlier phase of hepatization the appearance of the paren-

chyma on section is smooth, moist, and almost structureless. Later, with the contraction of fibrin, the plugs of alveolar exudate tend to protrude from the air sacs and impart a granular appearance (Figs. 549 and 550). Softening of the fibrin permits the plugs to be scraped away on the knife edge as minute granules, but the state of softening belongs strictly to the fourth stage. Some observers (Loeschke) have described a variable degree of intra-alveolar hemorrhage, concomitant with retraction of fibrin and relaxation of pressure on the capillaries. This is irregular and variable, seldom resulting in homogeneous red coloration of the tissue comparable with that of early hepatization.

STAGE 4.—Resolution. No definite time limits can be stated for the onset of resolution for it depends upon several variable factors. It occurs earlier in mild than in severe infections, earlier in previously immune than in nonimmune individuals, and it can be hastened by specific therapy. The process consists of liquefaction and absorption of the solid constituents of the exudate, but before this can take place, the bacteria must be destroyed. Liquefaction of the exudate usually begins in the oldest part of the lesion and progresses in spotty fashion toward the areas of more recent origin.

The first histologic evidence consists of an increased number of macrophages in the spaces between the alveolar walls and the plugs of intra-alveolar exudate. As the macrophages increase in number, the masses of fibrin shrink in size, apparently dissolving from the periphery. At the time the macrophages have become conspicuously numerous in an area, pneumococci have disappeared from the exudate. This fact and the reason for it have been demonstrated experimentally by Robertson and associates.⁹³ Macrophages in the presence of specific opsonin will phagocytize and completely destroy pneumococci much more rapidly and more completely than will polymorphonuclear cells under similar conditions. It has been generally assumed in the past that the enzymes of polymorphonuclear leukocytes were chiefly responsible for liquefaction of pneumonic exudates, but no correlation between their number or rate of disintegration and the disappearance of exudate has ever been

observed. Leukocytes of the polymorphonuclear variety will themselves die and disintegrate when the hydrogen-ion concentration of the medium changes slightly to the acid side of pH 7.0 and their enzymes are inactive in an acid medium,^{94, 95} while macrophages remain active until a pH of 6.5 is reached.

Evidence of resolution may be found as early as the third day in a successful tissue response in man and at any time after two days in canine pneumonia⁸⁹ and murine pneumonia.⁹¹ In the older parts of the lesion, resolution progresses even while the process is extending to involve new areas. The clinical crisis cannot be correlated in any way with resolution but corresponds more exactly with the time of arrest of the process and destruction of the great majority of the bacteria, with relief of the intoxication. Resolution and reexpansion usually require an additional one to three weeks after the time of the crisis. Absorption of liquefied exudate takes place through lymphatic and blood channels. Since it begins in the parenchyma and extends to the bronchioles and small bronchi much later, because of the greater time required for macrophages to migrate to their lumina in quantity, obstruction of the tubes by fibrin and leukocytes persists for some time after the parenchyma is free from exudate. This produces and maintains a state of atelectasis until the bronchial plugs are softened and absorbed or expelled.

The gross appearance of the lung during resolution is difficult to describe. It is often mistaken for edema and atelectasis or early consolidation. The tissue is no longer firm. The fibrin on the pleural surface remains and may exhibit evidence of beginning organization (slightly adherent). On section, the tissue is dark red to gray-red and translucent, having an edematous or gelatinous appearance. Dark red fluid resembling blood-stained pus exudes from the parenchyma and in it there may be small granules of undissolved fibrin. When most of the exudate has been absorbed but before re-expansion has occurred, the appearance is simply that of atelectasis and hyperemia with more or less edema.

Throughout the course of the pneumonia the bronchial mucosa of the involved lobe or lobes is moderately

hyperemic and often shows petechial hemorrhages, but severe damage to the membrane is exceptional. Only in the small bronchi and bronchioles does desquamation of epithelium occur to any great extent. By the time resolution is complete, the destroyed epithelium has regenerated. This requires about two weeks in experimental pneumonia.

Failure of Resolution.—Since we do not understand the chemical mechanism of resolution, it is impossible to explain exactly why, instead of undergoing complete liquefaction and absorption, the exudate of pneumonia occasionally becomes organized. It has never been proved that pure pneumococcal infections in the human lung can be organized. In experimental pneumococcal pneumonia it does not occur, but Wadsworth⁹⁶ was able to obtain organization of the intra-alveolar exudate in a diffuse lesion in canine lungs by injecting a mixture of pneumococci and staphylococci. It is well known that organization frequently takes place in the presence of infective agents which are not readily destroyed by macrophages such as tubercle bacilli, staphylococci, actinomycetes and other fungi, in the lesions of chemical pneumonia and in large infarcts where necrosis of tissue is extensive. Until more precise information is available from human cases, it seems wise to accept the view that organization may take place in certain mixed infections but to leave unanswered the question of organization in pure pneumococcal pneumonia.

When organization does occur, the involved portion of the parenchyma loses its function. Air does not enter the alveoli which are occupied by fibrous tissue. The sponginess of normal lung is replaced by a fleshy consistency ("carnification") and the color is changed to gray or yellowish-gray, depending upon the number of lipid-filled macrophages remaining in the tissue. Microscopically, streaming bundles of fibroblasts, in the early stage, or of mature collagenous tissue occupy all or most of the air spaces, passing through the interalveolar pores and continuous with similar masses in the alveolar ducts and respiratory bronchioles. Nests of pigment-filled macrophages are found in small clefts left by contraction of the exudate between alveolar walls and fibrous tissue.

Complications.—The principal complication is empyema. Serofibrinous exudation in the pleural space is a constant accompaniment of pneumococcal pneumonia and is not considered as a complication. If the pleura becomes heavily infected, the exudate becomes frankly purulent. The occurrence of empyema is suggested by persistence of fever beyond the usual five to ten days or by a recrudescence of signs of intoxication and a secondary rise of temperature within a few days after temporary relief of symptoms and diminution of fever either by lysis or by crisis. It is much less common in cases which have been adequately treated by serum, sulfonamides, or penicillin. The anatomical result, if the patient survives, is a thick, shaggy

pleural exudate which heals by organization, leaving a greatly thickened, dense, fused pleura (Fig. 548).

Abscess formation occasionally occurs in pure pneumococcal infections but is more commonly due to mixed infection with staphylococci or streptococci. Type III pneumococci in either lobar consolidation or bronchopneumonia have a tendency to cause necrosis of alveolar walls in small areas with formation of numerous small abscesses. These are seen at necropsy but are not visible in x-ray films.

Purulent pericarditis occurs by direct extension from a pleural empyema through the pleuro-pericardial membranes and constitutes a serious and usually fatal complication. The inflammatory reaction is closely similar to purulent inflammation of pleura or other serous membranes. Resulting fibrous adhesions, should the patient survive, are a serious handicap to cardiac function and lead to general hypertrophy of the myocardium.

Peritonitis as a complication in pneumonia is rare in adults but may occur as a direct extension of pleural empyema through the diaphragm. In children it is thought that the peritoneum is involved more often by the hematogenous route than by direct extension.

Endocarditis is an uncommon but usually fatal result of pneumococcal bacteremia or pyemia. The mitral and aortic valves and, less frequently, the tricuspid leaflets are the sites of bulky pink or greenish-gray thrombi which interfere with closure of the valves and give rise to emboli.

Purulent meningitis was responsible for the fatal termination of a numerically important portion of cases of lobar pneumonia before the general use of specific serum, sulfonamides, and penicillin, but appears to be less serious at present. It is part of persistent pneumococcal bacteremia, occurring in the most severe infections, and not infrequently is associated with thrombotic endocarditis. The leptomeninges are involved diffusely by symmetrically distributed exudate most abundant around the vessels in the sulci of the convexity but in time showing heavy deposit of gray exudate over the entire surface. The heavier deposits may have a yellowish or faintly greenish cast.

Pneumococcal arthritis is part of the results of hematogenous dissemination of pneumococci in a small percentage of cases. Infection of the synovial membrane of a large joint results in serous exudation into the cavity, if mild, or in intense inflammatory swelling of the soft tissue, erosion of the cartilages and production of copious purulent exudate, if severe.

Streptococcal Pneumonia

In infants, streptococcal infections of the bronchi and lungs may appear as primary bacterial diseases, but in older children and in adults, streptococci are coming to be thought of as secondary invaders, usually superimposed upon measles or influenza. No specific serologic types of streptococci have been in-

criminated. In epidemics, hemolytic streptococci are usually found to predominate. The combined effects of virus and streptococci are profound and frequently fatal. In fatal cases, the mucosa of larynx, trachea, and bronchi is swollen, diffusely reddened, and often is partly covered by a false membrane of exudate mixed with necrotic mucosa. Necrosis of the mucosa leads to the formation of ragged ulcers and to deep invasion of the soft tissues (cellulitis). The bronchioles are thickened and their lumina filled with mucopurulent exudate and necrotic epithelium.

In the pulmonary parenchyma the lesions almost invariably take the form of a symmetrical hemorrhagic bronchopneumonia, involving the lower parts of the lungs more extensively than the upper portions. Areas of consolidation are moist, dark red, poorly defined, and often coalescent. The exudate is poor in fibrin, in contrast to that usual in pneumococcal infections, and consists largely of plasma, erythrocytes and leukocytes. When the course is more prolonged, there is a tendency for organization of the exudate to occur, especially around the terminal bronchioles. This, together with the thickening of the walls of bronchioles and adjacent alveoli, produced by infiltration with mononuclear cells, results in the histologic pattern which suggested to MacCallum⁴⁸ the term "interstitial bronchopneumonia."

Staphylococcal Pneumonia

Most of the recorded cases of staphylococcal pneumonia have occurred during major epidemics of influenza. The staphylococcus is not a primary invader of the lung, but its presence seriously complicates other infections. It is usually present in exudates when abscess formation is a prominent feature. It is found in pure culture or as the predominant bacterium in as high as 10 per cent of primary pneumonias of children.⁹⁷ The term "primary pneumonia," as used here, is to distinguish the lesions from those of staphylococcal pyemia with secondary involvement of the lungs, and does not exclude viral infection of the respiratory tract as a possible factor in preparing the tissues for bacterial invasion. Occasionally, the lesions assume a lobar form, but usually these have the form of confluent bronchopneumonic lesions. The lower lobes show the more extensive consolidation in bronchogenic infections.

Areas of consolidation are firm, gray or gray-brown, mottled with hemorrhages or diffusely hemorrhagic. The older lesions show central necrosis with abscess formation, beginning with

necrosis of walls of bronchioles and enlarging by progressive involvement of wider zones of the parenchyma. In cases which follow a chronic course, the abscesses become coalescent to form honeycomb-like cavities through the areas of exudative consolidation, and the intervening tissue undergoes fibrous organization. This is one of the forms of "organizing pneumonia" or "carnification" of the lung. Involvement of the pleura with the development of staphylococcal empyema is frequent in children but uncommon in adults.

Tularemia

The mortality of tularemia has been estimated at about 5.6 per cent by the United States Public Health Service and twice as high in some of the other estimates (Simpson,⁹⁸ 11 per cent; Terry and Reichle,⁹⁹ 13 per cent). One-half to two-thirds of the fatal cases show extensive pulmonary involvement. The lungs are infected secondarily as a result of the bacteraemia commonly occurring in ulceroglandular tularemia. Early, the pulmonary lesions are clearly embolic, involving the two lungs more or less equally, with masses of consolidation which usually exhibit yellowish-gray masses of necrosis in their centers, surrounded by wide zones of hemorrhage and edema. When lesions have enlarged and coalesced, it is difficult to recognize their hematogenous origin, and, to complicate the picture, intrabronchial extensions occur as well. Early, the exudate consists of fluid, fibrin, and leukocytes, followed by necrosis of alveolar walls and of the cells of the exudate. Later, the leukocytes in the nonnecrotic areas are replaced by large mononuclears of the macrophagic type. Macroscopically the lesions may resemble tuberculous bronchopneumonia with caseation but histologically the resemblance is not so close. Epithelioid cell transformation is not pronounced in pulmonary tularemia though tubercle-like nodules with occasional giant cells are frequently present in lymph nodes. Hemorrhage and edema at the peripheries of actively extending foci are fairly common. The bronchopulmonary and tracheobronchial lymph nodes are less severely involved but show essentially the same type of lesions as are found in the nodes which drain the site of the primary cutaneous infection. (See also page 224.)

SPECIAL FORMS OF BACTERIAL INFECTION, NONSPECIFIC ETIOLOGY

Bronchopneumonia.—This term is applied to a purely morphologic conception of inflammation of bronchi and lungs. Its use is appropriate in a descriptive sense to all acute and chronic lesions of the bronchial tree associated with inflammatory exudation into the air spaces of the parenchyma. A wide variety of injurious chemical agents when inhaled as gases, fumes, aerosols, liquids, or dusts

Fig. 552.

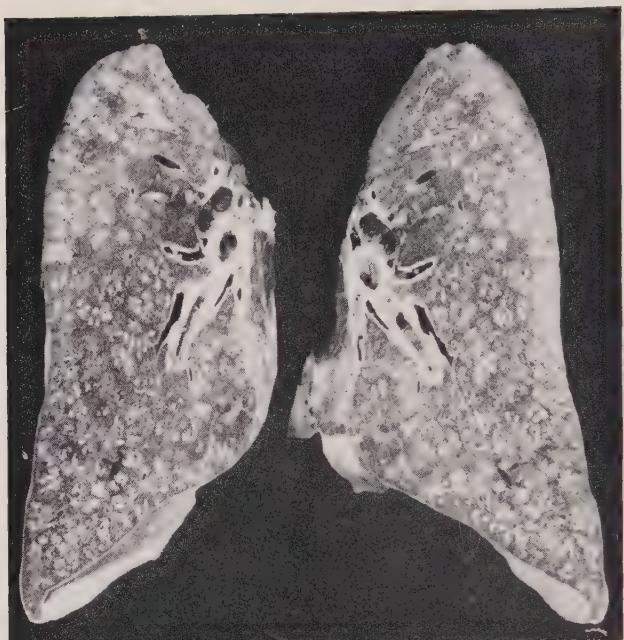


Fig. 553.

Fig. 552.—Bronchopneumonia. The peribronchiolar pattern is similar to that of tuberculous bronchopneumonia. (Specimen in F. R. Zeit Museum of Pathology, Northwestern University.)

Fig. 553.—Confluent bronchopneumonia.

(pneumoconiosis), as well as numerous bacteria, viruses, rickettsiae and fungi, are capable, either alone or in combination, of causing injury to the mucosal lining of bronchi and bronchioles, followed by exudation into the air spaces. Aspiration of fluids from mouth and pharynx, for example, vomitus, will lead to chemical injury and bacterial infection (aspiration pneumonia). Actively progressive pulmonary tuberculosis, since it is usually spread by the intraluminal dissemination of infective exudate to previously uninvolved parenchyma, is commonly of the form of an exudative or, later, a granulomatous bronchopneumonia. In primary viral infections of the

precipitously diminished. Pneumococci, particularly those of the less virulent types (see page 207), are often the predominant microorganism; they are found also in various mixtures with streptococci, staphylococci, *H. influenzae*, *K. pneumoniae* (page 211), and bacilli of the colon group.

The lesions are characteristically multiple and focal or patchy, frequently expanding to form larger coalescent masses of consolidation (confluent bronchopneumonia) (Fig. 553). The form, type of exudate and extent of the lesions of bronchopneumonia are determined largely by the nature of the exciting agents and, therefore, in previous discussions in this chapter, their consideration has been based

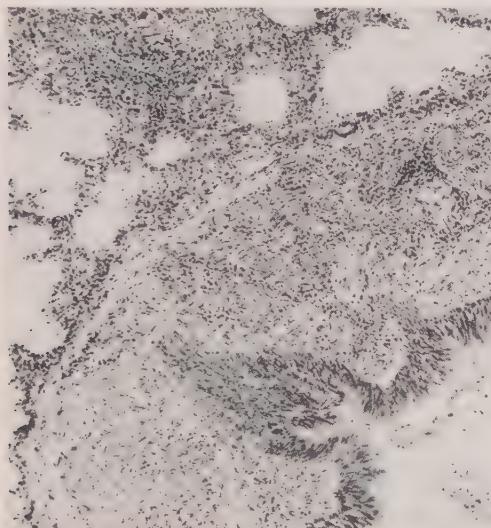


Fig. 554.

Fig. 554.—Pertussis. Thickening of wall of bronchiole; "interstitial" pneumonitis.

Fig. 555.—Pertussis. Alveolar walls are thickened; intra-alveolar exudate consists of fibrin and mononuclear cells. (See also Fig. 155, page 229.)

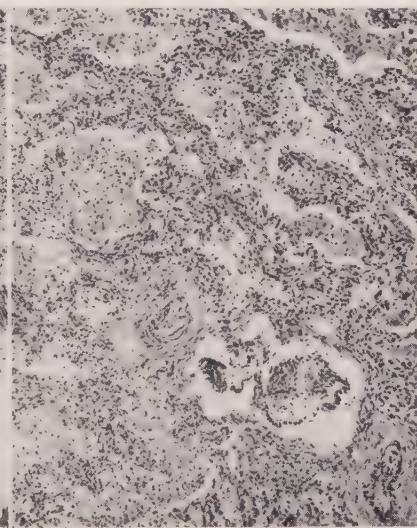


Fig. 555.

lung, complicated by secondary bacterial invasion, the pattern is similar but may be modified by conspicuous thickening of the alveolar septa which adjoin the involved respiratory bronchioles ("interstitial bronchopneumonia," see page 666).

With the introduction and wide usage of effective chemical and antibiotic agents in pulmonary infections, the classical primary or lobar form of pneumococcal pneumonia has become much less frequent at the autopsy table while the secondary bronchopneumonias occurring sporadically or in epidemics have not ap-

peared. (See also the sections on pulmonary lesions in Chapter 10, Bacterial Diseases, and in Chapter 14, Rickettsial and Viral Diseases.)

Hypostatic Pneumonia.—Congestion and edema, developing in the dependent portions of the lungs as the result of inadequate circulation of blood, from cardiac deficiency or vascular collapse, provide a favorable culture medium (edema fluid) for the growth of bacteria. Usually these are the common flora of the mouth and upper respiratory tract and, being of low virulence, often do not

excite a vigorous inflammatory exudative response. The exudate contains leukocytes and extravasated erythrocytes, is poor in fibrin, and merges imperceptibly with the diffusely edematous tissue within which it arises. The areas of consolidation are commonly located in the dorsal or dorsolateral portions of one or both lungs. The distribution may be patchy and irregular but bears no definite spacial relationship to the bronchial tree. Most of the "terminal pneumonias" (except bronchopneumonia following aspiration) which develop after prolonged shock, anesthesia, extensive surgical operations, and debilitating diseases leading to circulatory deficiency belong to this category. (See also page 647.)

The distribution of lesions differs from that of bronchogenic infections. When numerous and small, the lesions show a symmetry and uniformity of distribution not encountered in bronchopneumonia. More lesions are set just beneath the pleura than elsewhere in the parenchyma. Larger emboli are arrested in more central locations, leading to the formation of fewer but larger foci. If the larger arteries are obstructed by infected emboli, infarction may constitute the first stage of the process. Bacteria migrate from the central focus after damaging the arterial wall and a diffuse inflammatory process spreads in all directions from the site of the infarct.

The pyogenic bacteria most commonly encountered in hematogenous infections of the lung are streptococci (thrombophlebitis arising in veins of legs or pelvis) and staphylococci (furuncles, carbuncles, suppurative osteomyelitis, etc.). With the exception of distribution, the pneumonic processes excited by these

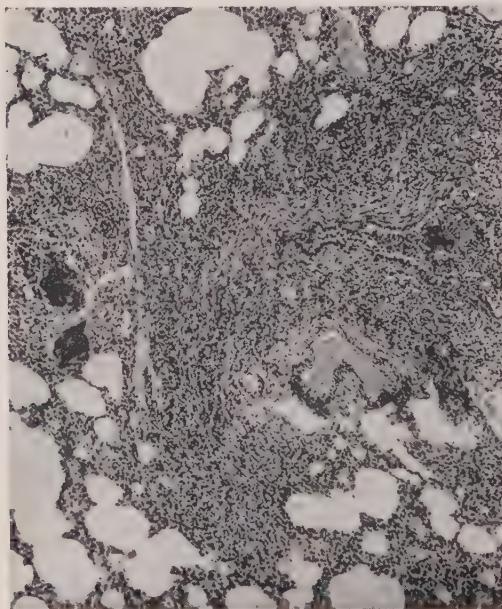


Fig. 556.

Fig. 556.—Giant cell formation in chronic bronchitis and bronchopneumonia (staphylococcal) of an infant.

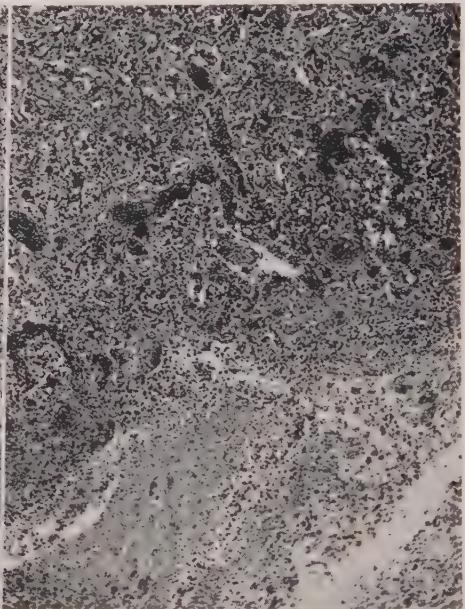


Fig. 557.

Fig. 557.—Embolic abscess. Vascular granulation tissue and collapsed parenchyma form the wall.

Embolic Pneumonia.—Inflammatory processes in the lung which are initiated by the arrest of masses of pathogenic bacteria in pulmonary arteries, arterioles, and capillaries, with the production of exudate in the parenchyma, are termed "embolic pneumonia" or "hematogenous pneumonia." If necrosis and liquefaction occur in the lesions, as in most staphylococcal and some streptococcal infections, the distinction between embolic abscesses with collateral pneumonia and embolic pneumonia with central abscess formation is highly artificial.

bacteria are similar to those resulting from bronchial dissemination, but the bronchi are involved only as a result of direct contact and perforation of their walls by parenchymal abscesses.

Pulmonary Abscess.—Abscesses of the lungs differ from abscesses of other tissues in that they develop in a spongy aerated tissue, often spread by intracanalicular extension, and may gain access to the lumina of larger bronchi so that they drain freely to the outside. There are two principal modes of origin. Embolic ab-

Fig. 558.



Fig. 559.

Fig. 558.—Multilocular abscess of lower lobe, communicating with large bronchus. Encapsulated empyema. (Specimen in F. R. Zeit Museum of Pathology, Northwestern University.)

Fig. 559.—Actinomycosis of right lower lobe and chronic empyema. (Clinical diagnosis was carcinoma.)

cesses are commonly multiple, bilaterally distributed, and caused by pyogenic cocci, principally staphylococci and streptococci. Since these are only a part of a general pyemia, the mortality is extremely high.

More important from the clinical standpoint are the bronchogenic abscesses which occur in solitary form or, if multiple, commonly are confined to a single lobe. Some arise acutely as the result of aspiration of infective fluids into the bronchial rami and parenchyma of the lung. Others arise insidiously from ulceration of the lining of dilated bronchioles in the presence of long-standing bronchitis and bronchiectasis.

Rare modes of abscess formation are direct traumatic injury as by puncture of the lung incidental to fracture of ribs and direct extension of amebic abscess of the liver through the diaphragm into the base of the lung.

PUTRID ABSCESSSES.—Most bronchogenic abscesses which are recognized during the life of the patient are of the "putrid" type. No one bacterial agent can be considered as specific since none is constantly present in putrefying lesions of the human lung and most of them are harmless when pure cultures are injected into animals. Anerobic bacteria are usually found in the lesions in various mixtures with pyogenic cocci. Anaerobic or facultative anaerobic streptococci, staphylococci, fusiform bacilli, spirillae, diphtheroids, *B. necrophorus*, *B. melaninogenicus*, and various unidentified gram-negative bacilli have been reported by different authors.

A large proportion of the abscesses follow surgical operations on the mouth, jaw, or nose, and especially after tonsillectomy or extraction of teeth under general anesthesia.¹⁰⁰ Stern¹⁰¹ found that gross infection of gums and teeth was an important association. The distribution in the lungs favors the right rather than the left, but the right upper lobe and right lower lobe are involved with about equal frequency. The lesions of the lower lobe are more commonly found in the apex of the lobe rather than in the basal portion.¹⁰²

MORBID ANATOMY.—There is rapid destruction of bronchi, blood vessels, and parenchyma, with the production of foul pus, which gains access to large bronchi and begins to drain in about ten days to two weeks. The walls of the abscesses are formed by zones of consolidated parenchyma and lined by exceedingly ragged necrotic tissue. The form is quite irregular but conforms roughly to the distribution of groups of lobules. Acute abscesses are multilocular (Fig. 558) but gradually assume rounded form and develop a fibrous capsule if they become chronic.

Gangrene of the Lung.—This is a term which is commonly misused and, at best, is poorly defined. Rapidly spreading abscesses of the lung which emit a foul odor due to putrefaction are often termed "gangrene of the lung" but are, more accurately, "putrid abscesses." The term "gangrene" might well be reserved for a process of massive necrosis resulting from ischemia, whether or not the necrosis is followed by putrefaction. Failure of nutrition is therefore the determining factor as in gangrene of the extremities. Statistics relating to pulmonary abscess and gangrene are contradic-

tory as a result of the failure of many authors to define clearly the process under consideration. In some publications the lesions which produced exudates with a foul odor and associated with fusospirochetal organisms were classified as gangrene and those without offensive odor as abscess. This is obviously an unscientific approach to the subject since the invasion by saprophytes is a secondary, accidental phenomenon. An etiological classification is highly desirable but impossible in the present state of knowledge.

FUNGUS DISEASES OF THE LUNG

Actinomycosis.—Pulmonary infection by the ray fungus (*Actinomyces bovis*) usually takes place by the bronchial route. The lesions occur much more frequently in a lower than in an upper lobe. Some are secondary and the result of aspiration of exudate from lesions of face or neck which open into the mouth. Others occur by aspiration from a normal mouth or pharynx and perhaps by direct inhalation of fungi from the air. The majority of cases occur in young men, especially farmers, greenhouse workers, and others who have frequent opportunities to inhale dust from grain or straw. In the early stages of the disease, as in tuberculosis, there are no symptoms. By the time the earliest symptoms have appeared, most commonly cough or pain in the chest, the process is far advanced. Most cases of pulmonary actinomycosis are recognized for the first time by postmortem findings. It is ordinarily an indolent process, gradually extending from one lobule to another until a major portion of a lobe is involved.

The lesion found at autopsy may be of the nature of a diffuse yellowish gray granulomatous consolidation with scattered groups of small abscesses filled with gray pus (Fig. 559). Minute gray or yellow granules usually can be found by careful examination of the pus and recognized by microscopic examination as colonies of fungus. More extensive abscess formation results in the appearance of a coarse honeycomb with walls of dense fibrous tissue. Extensions through the thoracic walls and perforation to the cutaneous surface are relatively common. The pleura is thick and leather-like in old lesions. The formation of intrapleural abscesses or massive empyema is usual. Extension through the diaphragm into the liver sometimes occurs, and it may be impossible to determine whether the hepatic abscesses followed primary pulmonary infection or were the result of portal extensions from primary infection of the cecum; followed by extensions into the base of the lung.

The fungi are occasionally found in the sputum of patients with abscesses in the lung and more often in the exudate of sinuses leading through the body wall to the surface. Numerous free-hand sections through the granulomatous lesions may reveal small cavities which contain pus and the pathognomonic "sulfur" granules. Sometimes it is necessary to make microscopic sections from numerous areas in order to demonstrate the colonies of ray fungi. The structure of the granulation tissue itself is not specific. Even the abscesses are

similar to those of chronic staphylococcal infections and are surrounded by dense masses of large and small mononuclear cells, epithelioid macrophages, and rare multinuclear giant cells. Older lesions are characterized by the presence of irregularly arranged masses of collagenous tissue. There is no tubercle formation and necrosis is characteristically liquefactive. With localization of actinomycosis in the lower lobes there is less difficulty in differentiating it from tuberculosis than from nonspecific chronic abscess of bacterial origin or from bronchial carcinoma. (See also page 343.)

Blastomycosis.—The lung is involved by inhalation of the spherules or by blood stream metastasis from a cutaneous lesion. The latter is the commonest site of primary infection by this yeastlike fungus. The lesions, which at first appear as small discrete nodules, enlarge by direct extension, become coalescent and undergo coagulative necrosis in the center, sometimes simulating the caseation of tuberculosis.

a granular center. Budding forms serve to differentiate the organisms from coccidioides which reproduce by endosporulation. In active blastomycosis of the lungs, the fungi can usually be found at some time in the sputum. Since the cells stain poorly, examination in unstained preparations of sputum treated with 20 per cent sodium hydroxide is best for their identification. (See also page 345.)

Coccidioidomycosis.—Eighty per cent of reported cases of infection by *Coccidioides immitis* have come from the San Joaquin Valley in California. The disease occurs in those whose occupations are close to the soil, such as well drillers, farmers, fruit and cotton pickers, and especially in those occupied in the grape industry. Pulmonary infections occur in two clinical forms, the acute inflammatory episode, usually self-limited and known as "valley fever," and the granulomatous form in which the mortality is high, reaching 50 per cent or more.



Fig. 560.

Fig. 560.—Actinomycosis. Low-magnification photomicrograph. Fibrous thickening of alveolar and bronchiolar walls; organization of exudate.

Fig. 561.—Actinomycosis. Colony of ray fungus in an abscess from same lung as Figs. 559 and 560. Higher magnification than Fig. 560.

Numerous small cavities are found in the late stages of the process, but large cavities such as those of chronic tuberculosis do not occur. When extensive, the gross form of the lesion is that of a confluent bronchopneumonia. Histologically the masses of consolidation are composed largely of mixtures of large mononuclear cells, lymphocytes, and fibroblasts, with a generous scattering of multinucleated giant cells. Where necrosis has occurred, polymorphonuclear neutrophiles are numerous and the abscesses may contain liquid pus. The fungi are found most readily in the solid portions of the lesions, in the cytoplasm of large epithelioid mononuclear cells or multinuclear giant cells. They are recognized as spherical or oval bodies, 7 to 12 microns in diameter, with a clear refractive cell wall and

In the latter, the lesions take the form of granulomatous bronchopneumonia. The lesions closely resemble those of tuberculosis with abundant formation of multinucleated giant cells, caseation, and calcification of necrotic centers. Calcified foci may be mistaken in the x-ray film for tuberculous nodules. A negative tuberculin test and positive reaction to coccidioidin are necessary to establish with reasonable certainty the identity of such calcified lesions as coccidioidal granuloma. In active cases, the spherules of coccidioides may be found and identified in the sputum. (See also page 348.)

Histoplasmosis.—This is a widespread infection of human beings, but its incidence varies greatly from one area to another. In the United

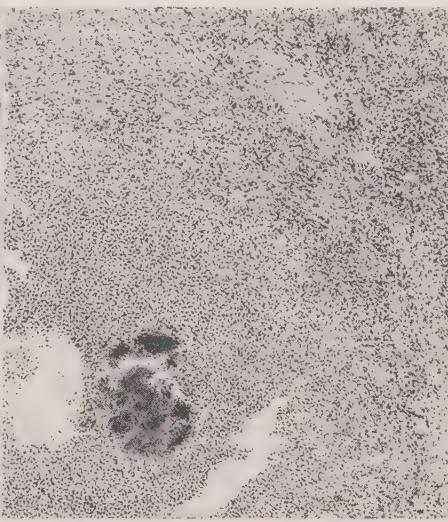


Fig. 561.

States most cases occur in the central portion of the eastern half of the country. A survey by Palmer¹⁰³ of the United States Public Health Service demonstrated that there may be numerous otherwise unrecognized cases of sensitivity to histoplasma products with pulmonary calcification among individuals studied with cutaneous sensitivity tests. These constituted about 25 per cent of 3,000 student nurses in Detroit, Minneapolis, Kansas City, and Philadelphia. The incidence of lung calcifications was much greater in those with positive reactions to histoplasmin and negative tuberculin than with positive tuberculin and negative histoplasmin tests.

The cellular response in histoplasmosis is similar to that in leishmaniasis and consists of hyperplasia of tissue macrophages in all of the involved tissues, particularly of liver, spleen, and lymph nodes. In the lungs, the lesions tend to form nodules as in miliary tuberculosis. The fungus is a small ovoid yeastlike cell measuring from 1 to 4 microns in diameter and found in large numbers within the cytoplasm of the swollen pale macrophages. (See also page 346.)

NEOPLASMS OF THE RESPIRATORY TRACT

Bronchial carcinomas are not only the most important primary neoplasms of the lungs with respect to clinical malignancy but in some institutions they are now the most common of all deep-seated cancers. Cancer of the larynx also appears to have increased in incidence and is about one-seventh as common. Metastatic cancers of the lungs and mediastinum are of importance chiefly in differential diagnosis. Tracheal neoplasms are surprisingly rare in view of the close similarity between the epithelial lining of the trachea and of the large bronchi which are so frequently the site of carcinoma. Tumors of the nose and pharynx are discussed on pages 705, 706, and 708.

Bronchial Carcinoma.—

HISTOGENESIS AND CELL TYPES.—Most of the malignant tumors arising from the bronchopulmonary tissues develop as single or multiple foci of malignant metaplasia of the columnar epithelium which lines the bronchial tree. The possible exceptions are those classified as bronchial adenoma (malignant adenoma) and pulmonary adenomatosis or alveolar cell carcinoma. The first observable change consists of hypertrophy, hyperplasia and loss of polarity of the mucosal epithelium, followed by infiltration of the underlying fibrous stroma and slight roughening and elevation of the luminal surface. Extension along the mucosal surface appears

to take place by transformation of contiguous epithelium into cancerous cells, rather than by its replacement; however, the superficial layer of mucosa is frequently undermined by the continuous extension of sheets and cords of tumor cells along the tunica propria and through the lymph channels. Often the malignant cells retain a certain resemblance to the relatively undifferentiated "reserve cells" which form the basal layer of respiratory epithelium, or become rounded and resemble the cells of lymphoid tumors. In other cases they become transformed into epidermoid cells (Fig. 564, A) which at times may form intercellular bridges and exhibit some degree of keratinization. Glandlike and tubulelike structures are fairly common in those tumors which retain the columnar or cuboid form of their cells of origin (Fig. 564, C). Occasionally these exhibit mucin-secreting capacity (mucinous adenocarcinomas). There are all gradations between these histologic types, leading to differences of opinion with regard to the relative incidence of the various types and justifying the opinion of Willis¹⁰⁴ "that there is only one entity *carcinoma of the lung*, that individual tumors show various structural combinations, and that great pleomorphism is possible in one tumor." In general the cylindrical cell types, including the adenocarcinomas, are the least common in most reported series, while those classified as squamous cell carcinomas and those grouped as pleomorphic or undifferentiated cell tumors form the two large classes. Many pathologists include the small spindle cell ("oat cell") form and the round cell ("lymphoid cell") form with the large group of undifferentiated cancers (Fig. 564, B and D).

GROSS FORMS.—By far the greatest number of bronchial carcinomas arise in the primary and secondary bronchi (Fig. 565) and consequently will appear upon x-ray examination as more or less bulky densities in the region of the hilum. With obstruction by encirclement of the bronchus or by polypoid extensions into the lumen (Fig. 566), atelectasis of the parenchyma occurs distal to the site of obstruction. Bronchiectasis is especially common in those cases where the stem bronchus of a lower lobe is involved and accumulation of secretion and exudate has resulted from

prolonged bronchial obstruction. The clinical signs and symptoms of the disease, chest pain, cough, dyspnea, fatigue, and hemoptysis, will be determined by the location of the tumor and by the degree of bronchial obstruction, necrosis, and ulceration. The peripherally situated cancers and diffusely infiltrating forms are usually symptomless until they have reached an advanced stage because of the lack of involvement of large bronchi. In rare instances, carcinoma of an upper lobe may extend to the parietal pleura and

from 1.0 to 2.5 per cent of all autopsies and 8 to 20 per cent of all cancers in American hospitals. In some British hospitals it is reported to constitute one-fifth to one-third of all fatal cancers.¹⁰⁷ On the other hand, statistical analysis of several large series of autopsies¹⁰⁸⁻¹¹² has indicated that the rate of increase has not been significantly greater than that of cancer as a whole. In some series, a change in the nature of the hospital population such as an increased rate in the hospitalization of cancer patients,¹¹³ the predominance of male patients of the older age groups or special interest, and competence of the medical staff in the field of thoracic surgery¹¹⁰ may have increased the relative number of intrathoracic tumors which have been observed in these hospitals. Therefore, comparisons of



Fig. 562.—Carcinoma of bronchus.

structures of the upper mediastinum, involving the nerves of the thoracocervical chain and brachial plexus and producing a characteristic clinical syndrome ("superior pulmonary sulcus tumor"¹⁰⁵).

INCIDENCE.—Statistical studies of the incidence of cancer of the lung have led to conflicting conclusions. It appears to have increased progressively during the past half century to the extent of three- to tenfold. In some institutions it is now the most commonly encountered fatal malignant disease,¹⁰⁶ in others it is second only to cancer of the stomach or colon but, in general, it appears to be in third place, constituting

present incidence with that of the distant past are probably misleading since the latter appears to be much too low.

Even though we accept hospital statistics as approximately correct, the question of incidence in the general population cannot be answered at present since the hospital population is not representative. The figures from vital statistics are not yet sufficiently accurate to justify conclusions with regard to the relative incidence of deep-seated cancers, particularly bronchial carcinoma.^{113, 114} It is reasonably certain that in the past many cases of lung cancer have been inaccurately recorded as pulmonary tuberculosis, mediastinal tumor, or other lesions of the chest.^{104, 115}

AGE AND SEX.—About four-fifths of cases of bronchial carcinoma occur in the decades between 40 and 70 years with the peak of incidence in the middle fifties. All published series in recent years show a striking preponderance in men, the ratio varying from 2:1 to 5:1, and the ratio has become increasingly

employed in the chromate industry, in nickel refineries, in the manufacture of arsenical insecticides, in asbestos workers, in those exposed to radioactive gases and dusts, and to the inhalation of the vapors from some tars and oils.¹¹⁵ In the chromate extraction plants of America, the incidence has been reported as about sixteen times the expected ratio.^{116, 117} Similarly high figures have been recorded from the chromate industry in Germany.¹¹⁸ A high proportion of cases of cancer of the nasal passages and lungs has been recorded in workers exposed to volatile nickel carbonyl in two Welsh nickel refineries. Although arsenic is not a proved carcinogen for the lung, long exposure to arsenious oxide is known to produce chronic dermatitis, sometimes associated with epitheliomas of the skin and, less frequently, bronchial carcinoma (see Hueper¹¹⁵ for discussion and references). The number of cases of lung cancer associated with asbestosis is small but significantly greater than in other forms of pneumoconiosis. Silicosis is not a predisposing factor in neoplastic disease¹¹⁹ and coal miners have shown an incidence of lung cancer which was less than that of the general population.¹²⁰

Although traces of cancerogenic hydrocarbons are present in the tars of coal smoke and soot, there is no convincing evidence that the inhalation of soot-laden air is important in the amounts commonly encountered in the industrial cities. On the other hand, workers who have been exposed to the massive inhalation of fine particles of hot tar and to the distillation products of tar have exhibited a high incidence and at an unusually early age. The observation that cancer of the lung occurs more frequently in cigaret smokers than in other smokers and in nonsmokers of comparable age^{107, 121-123} has raised the question of tobacco smoke as a possible cancerogenic agent. In addition to tobacco tars, the puffed smoke of cigarettes has been found to contain arsenic as arsenious oxide in amounts of 3.3 to 10.5 mg. per cubic meter or about twice as much as in pipe smoke and more than three times as much as in cigar smoke.¹²⁴ So far, neither of these components has been proved experimentally to possess significant tumor-promoting effect in the lungs.

Of all of the types of occupational cancer, that which has followed prolonged exposure to the effects of ionizing radiation was the earliest recognized and one of the most intensively studied. The high incidence of some kind of fatal lung disease in the cobalt miners of the Schneeberg district in Saxony, Germany, was recorded more than four centuries ago but it was not until 1879 that it was properly diagnosed as some form of malignant neoplasm. When the first systematic investigation was undertaken in the early 1920s, it was found that about three-fourths of deaths among the miners were due to carcinoma of the lungs. In the workers of the radium mines of Joachimsthal, Czechoslovakia, about one-half of the deaths were attributed to lung cancer after an interrupted investigation which was begun in 1926. Besides radioactive matter, the dusts of the mines at Schneeberg contained principally silicates, arsenic, and cobalt, while the mine dusts at Joachimsthal contained a wide variety



Fig. 563.—Metastatic sarcoma (rhabdomyosarcoma arising in psoas muscle).

wider since little or no increase has been observed in women. In men the incidence has been increasing at a greater rate than has cancer of the stomach, colon, or prostate gland.

CAUSES.—A disproportionately high incidence of pulmonary cancer has been observed in men

of minerals including silica and occasionally arsenic, bismuth, nickel, cobalt, and uranium. A detailed account of the technical data, history of exposure, and other circumstances concerning the occupational cancers of these two mining areas has been reviewed by Hueper¹¹⁵ with the conclusion that the common factor is the presence of radioactive matter in the form of radon which in all probability was responsible for eliciting the neoplastic response in the lungs.

This view is supported by the fact that at Joachimsthal, two of the eleven affected workers were employed above ground in the radium laboratories.

METASTASES.—The earliest metastases of bronchial carcinomas are found, as a rule, in the bronchopulmonary lymph nodes, followed by lymphogenous involvement of

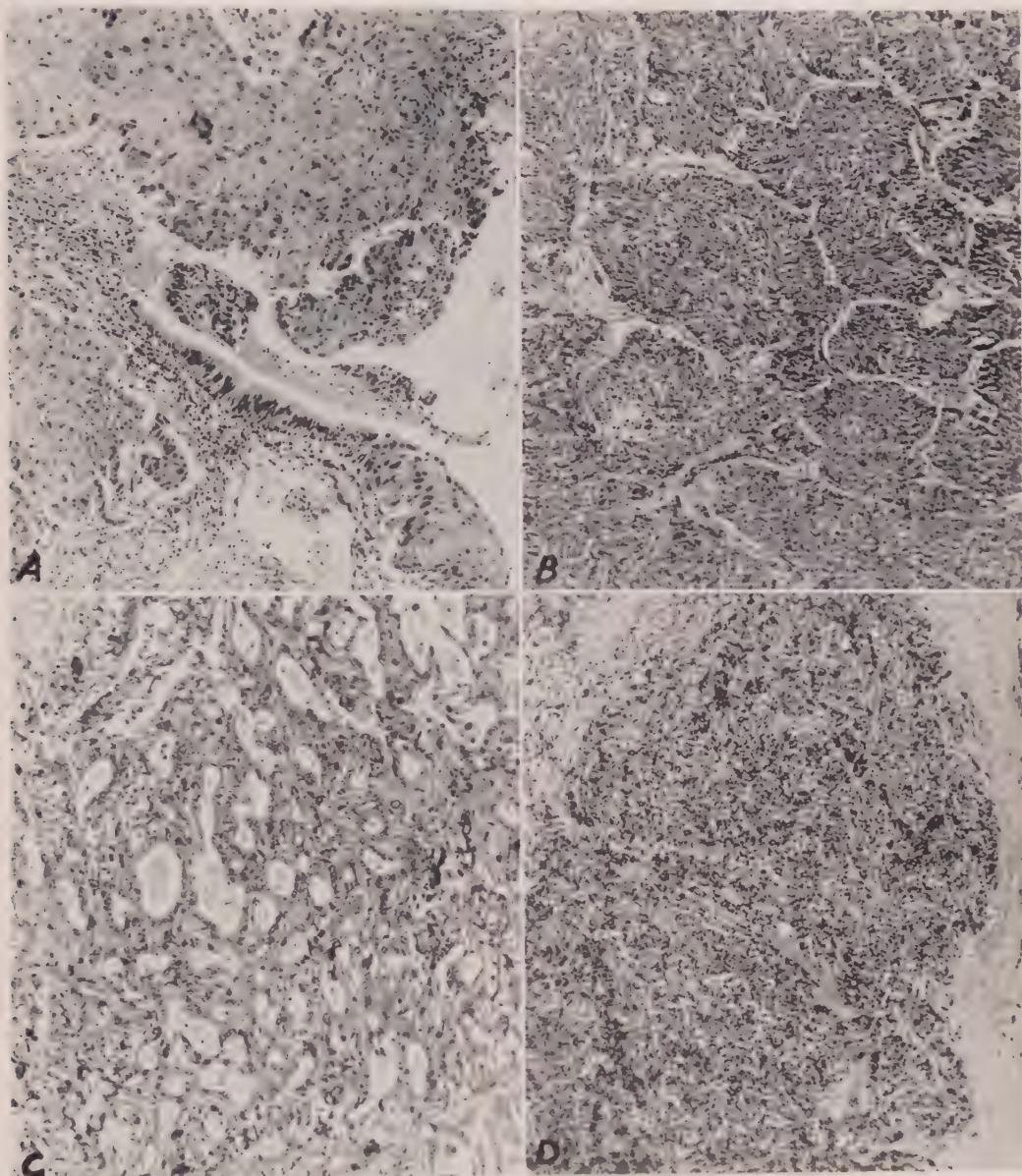


Fig. 564.—Photomicrographs of bronchial carcinomas, all at the same magnification. *A*, Squamous cell type in bronchial wall, showing apparent transition from normal ciliated columnar epithelium to neoplastic stratified squamous epithelium (lower one-third of figure). *B*, Undifferentiated carcinoma ("oat cell" type), filling alveolar spaces. *C*, Adenocarcinoma. Other portions of this same tumor showed a squamous cell type of picture and undifferentiated pleiomorphic cylindrical cell carcinoma. *D*, Small round cell carcinoma ("lymphoid cell" type).

the tracheobronchial and paratracheal nodes. The pleura, pericardium, heart, mediastinum, and diaphragm may be invaded by continuous extension of the primary tumor. Occasionally the local destruction of one or two vertebral bodies with spinal kyphosis is the first evidence of the presence of intrathoracic tumor.



Fig. 565.—Carcinoma of secondary bronchus in surgically resected lung.

In some cases the pleura is infiltrated early and the complete envelopment of the involved lung by a dense sheet of cancerous tissue often has been misinterpreted as pleural endothelioma, especially in those cases in which the intrapulmonary primary lesion was difficult to identify because of its small size or peripheral location. Hematogenous metastases are found in about three-fourths of cases at postmortem examination and may occur in almost any part of the body. The organs which are most commonly involved are the liver, bones, kidneys, adrenals, brain, thyroid, and spleen.¹²⁵ Not infrequently a metastatic tumor of the brain originating in a symptomless bronchial carcinoma is misdiagnosed as a primary cerebral tumor.

Metastatic cancers of the lung, most often originating in tumors of the stomach and breast, present difficult problems in diagnosis when they lie in close relationship to large bronchi or form a principal mass in the region of the pulmonary hilus. Among 109 such cases of metastatic tumors, King and Castleman¹²⁷ found 18.3 per cent to have invaded the walls of bronchi. The finding of cancerous tissue in a specimen from bronchial biopsy is not sufficient, therefore, to justify the conclusion that such a tumor has arisen in the lung.

Bronchial Adenoma (Malignant Adenoma).—These slowly developing tumors constitute about 5 per cent of primary neoplasms of the bronchi¹⁰⁴ and differ from other malignant tumors of the respiratory tract in their relatively low degree of malignancy, histogenesis, gross and microscopic appearance, and sex incidence. They appear to arise from the submucosal glands of the primary and secondary bronchi, rarely in the lower part of the trachea. The age at the time of development of symptoms is much earlier than in other bronchial carcinomas, most reported cases occurring in young adults. The two sexes are affected about equally. In seventy cases reviewed by Foster-Carter¹²⁸ the mean age at the onset of symptoms was 28 years, and 62 per cent were in females. The endobronchial portion of the tumor partially obstructs the lumen and leads to bronchiectasis distal to the site of obstruction. Hence the history frequently includes one or more attacks of "pneumonia," intermittent cough, becoming progressively more productive, and hemoptysis.



Fig. 566.—Polypoid intrabronchial portion of an extensive bronchial carcinoma, simulating a bronchial "adenoma."

The usual gross appearance is that of a smoothly rounded sessile polyp, protruding into the lumen of a large bronchus which in some cases is locally dilated. The mucosal covering usually persists but its respiratory epithelium often is altered by squamous metaplasia or by superficial erosion. Local invasion of the bronchial wall and of the peribronchial connective tissue and pulmonary parenchyma has usually occurred by the time the tumor is discovered and prevents its complete surgical removal by the endobronchial route. Metastasis to the hilar and mediastinal lymph nodes may be delayed for years after the onset of symptoms. Distant metastasis to the liver, brain, bone marrow, and other tissues has been recorded in a few cases.

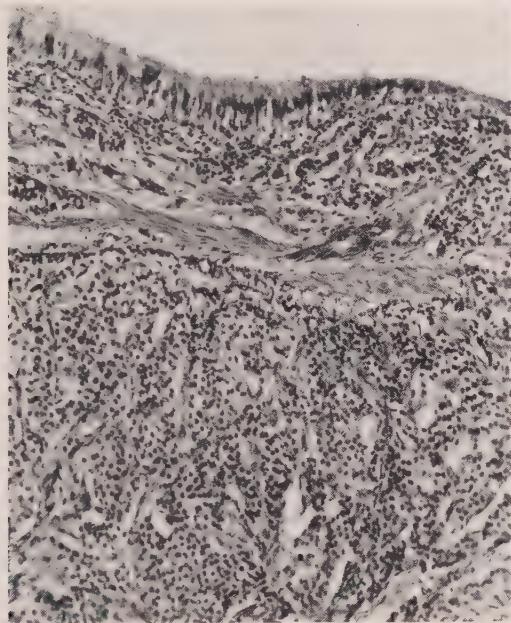


Fig. 567.

Fig. 567.—Bronchial adenoma (malignant adenoma) from surgically removed lung. Metastases were present in bronchopulmonary lymph nodes. Note intact respiratory epithelium on luminal surface.

Fig. 568.—Alveolar adenomatosis. Same magnification as Fig. 567. Alveolar walls form the stroma of the relatively large, mucin-secreting neoplastic cells.

The histologic structure varies in much the same manner as that of the so-called mixed tumors of salivary glands.¹²⁹ About one-third consist of glandlike structures with relatively abundant stroma which is moderately to highly vascular and sometimes hyalinized. A few resemble the basal cell tumors of the epidermis or carcinoid tumors of the intestinal tract but differ from the latter in that they do not exhibit argentaffin fibers or granules. The largest number, 60 per cent in Foster-Carter's series, show solid masses or anastomosing cords of small uniform epithelial cells with scanty cytoplasm and rare mitotic figures, separated by fibrous trabeculae (Fig. 567). All of these histologic pictures may be found in a single tumor.

Alveolar Carcinoma (Bronchiolar Carcinoma: Pulmonary Adenomatosis).—Since the first case report of a multiple nodular form of lung cancer by Malassez (1876) and a description of a case of the diffuse form by Musser (1903) numerous cases have been recorded but little has been added to the basic understanding of this entity. Malassez was uncertain as to whether the tumor arose from alveoli or from bronchioles and this question is undecided today. There seems to be little justification for a sharp distinction between those tumors which show neither invasion nor metastasis at the time of death ("adenomatosis") and those which have metastasized ("alveolar or bronchiolar carcinoma"). In spite of the fact that only a little more than one-half of the cases have

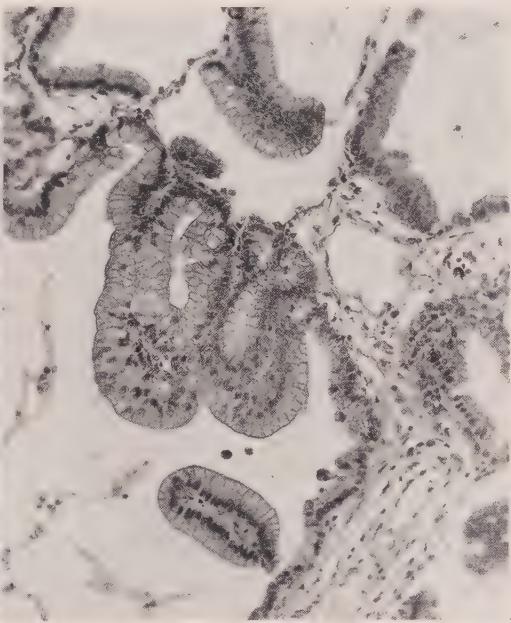


Fig. 568.

been reported to show regional or distant metastasis at the time of death, the mean survival time from the onset of symptoms is no greater and in some series apparently less than that in carcinoma of the larger bronchi. Many of the reported autopsy cases have succumbed to intercurrent pulmonary infection within a few months after the onset of severe symptoms. The prognosis is better when the disease is localized to one lobe since it is then amenable to surgical removal. In a recent report of 33 cases from Memorial Hospital in New York¹³⁰ 7 out of 16 patients were recorded as free of apparent disease six months to five years after surgical intervention, 2 having passed the five-year period.